(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 March 2001 (01.03.2001)

PCT

(10) International Publication Number
WO 01/14375 A1

(51) International Patent Classification[7]: C07D 471/04, A61K 31/437, A61P 35/00 // (C07D 471/04, 235:00, 221:00) (C07D 471/04, 231:00, 221:00)

(21) International Application Number: PCT/GB00/03139

(22) International Filing Date: 15 August 2000 (15.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9919778.2 21 August 1999 (21.08.1999) GB

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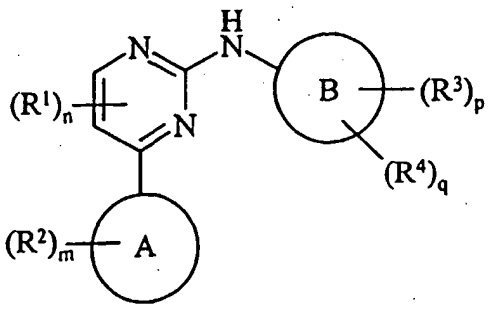
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: IMIDAZO[1,2-A]PYRIDINE AND PYRAZOLO[2,3-A]PYRIDINE DERIVATIVES



(I)

(57) Abstract: A compound of formula (I) wherein Ring A is imidazol[1,2a]pyrid-3-yl or pyrazolo[2,3a]pyrid-3-yl; R^2 is as defined within; m is 0-5; wherein the values of R^2 may be the same or different; R^1 is as defined within; n is 0 to 2, wherein the values of R^1 may be the same or different; Ring B is phenyl or phenyl fused to a C_{5-7}cycloalkyl ring; R^3 is as defined within; p is 0-4; wherein the values of R^3 may be the same or different; R^4 is as defined within; q is 0-2; wherein the values of R^4 may be the same or different; and wherein $p+q \leq 5$; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof is described. The use of compounds of formula (I) in the inhibition of cell cycle kinases CDK2, CDK4, and CDK6 are also described. Pharmaceutical compositions, methods and processes for preparation of compounds of formula (I) are detailed.

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IMIDAZO[1,2-A]PYRIDINE AND PYRAZOLO[2,3-A]PYRIDINE DERIVATIVES

The invention relates to pyrimidine derivatives, or pharmaceutically acceptable salts or *in vivo* hydrolysable esters thereof, which possess cell-cycle inhibitory activity and are accordingly useful for their anti-cell-proliferation (such as anti-cancer) activity and are therefore useful in methods of treatment of the human or animal body. The invention also relates to processes for the manufacture of said pyrimidine derivatives, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments of use in the production of an anti-cell-proliferation effect in a warm-blooded animal such as man.

A family of intracellular proteins called cyclins play a central role in the cell cycle. The synthesis and degradation of cyclins is tightly controlled such that their level of expression fluctuates during the cell cycle. Cyclins bind to cyclin-dependent serine/threonine kinases (CDKs) and this association is essential for CDK (such as CDK1, CDK2, CDK4 and/or CDK6) activity within the cell. Although the precise details of how each of these factors combine to regulate CDK activity is poorly understood, the balance between the two dictates whether or not the cell will progress through the cell cycle.

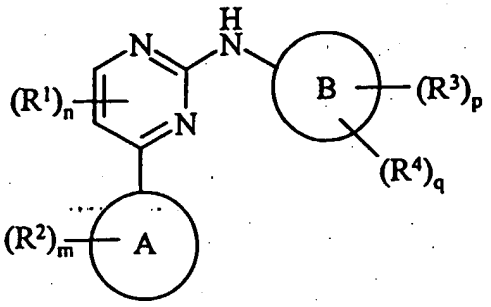
The recent convergence of oncogene and tumour suppressor gene research has identified regulation of entry into the cell cycle as a key control point of mitogenesis in tumours. Moreover, CDKs appear to be downstream of a number of oncogene signalling pathways. Disregulation of CDK activity by upregulation of cyclins and/or deletion of endogenous inhibitors appears to be an important axis between mitogenic signalling pathways and proliferation of tumour cells.

Accordingly it has been recognised that an inhibitor of cell cycle kinases, particularly inhibitors of CDK2, CDK4 and/or CDK6 (which operate at the S-phase, G1-S and G1-S phase respectively) should be of value as a selective inhibitor of cell proliferation, such as growth of mammalian cancer cells.

The present invention is based on the discovery that certain pyrimidine compounds surprisingly inhibit the effects of cell cycle kinases showing selectivity for CDK2, CDK4 and CDK6, and thus possess anti-cell-proliferation properties. Such properties are expected to be of value in the treatment of disease states associated with aberrant cell cycles and cell proliferation such as cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders , psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma,

acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Accordingly, the present invention provides a compound of formula (I):



(I)

wherein:

Ring A is imidazo[1,2a]pyrid-3-yl or pyrazolo[2,3a]pyrid-3-yl;

$\mathbf{R^2}$ is attached to a ring carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, phenyl, heterocyclic group, phenylthio or (heterocyclic group)thio; wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl or heterocyclic group may be optionally substituted on carbon by one or more G; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q;

m is 0-5; wherein the values of R^2 may be the same or different;

$\mathbf{R^1}$ is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-2}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl; wherein any C_{1-2}alkyl, C_{1-3}alkyl, C_{2-3}alkenyl or C_{2-3}alkynyl may be optionally substituted on carbon by one or more J;

n is 0 to 2, wherein the values of R^1 may be the same or different;

Ring B is phenyl or phenyl fused to a C_{5-7}cycloalkyl ring;

R^3 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^3 may be the same or different;

R^4 is a group A-E-; wherein

A is selected from C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl; which C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

E is a direct bond or -O-, -C(O)-, -OC(O)-, -C(O)O-, -N(R^a)C(O)-, -C(O)N(R^a)-, -N(R^a)-, -S(O)$_r$-, -SO_2N(R^a)- or -N(R^a)SO_2-; wherein R^a is hydrogen or C_{1-6}alkyl optionally substituted by one or more D and r is 0-2;

D is independently selected from oxo, halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, benzyloxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or phenyl may be optionally substituted on carbon by one or more K;

q is 0-2; wherein the values of R^4 maybe the same or different; and wherein $p + q \leq 5$;

G, J and K are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

Q and R are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

For the avoidance of doubt, the phrase "wherein any C_{1-6}alkyl is optionally substituted" and other such phrases also includes the possibility of optional substitution on other groups that contain a C_{1-6}alkyl group, for example a C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl or a *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C_{1-6}alkyl" includes C_{1-4}alkyl, C_{1-3}alkyl, C_{1-2}alkyl, propyl, isopropyl and *t*-butyl. However, references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals, for example "phenylC_{1-6}alkyl" includes phenylC_{1-4}alkyl, benzyl, 1-phenylethyl and 2-phenylethyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

A "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 4-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH_2- group can optionally be replaced by a -C(O)-, a ring nitrogen atom may optionally bear a C_{1-6}alkyl group and form a quaternary compound or a ring nitrogen and/or sulphur atom may be optionally oxidised to form the *N*-oxide and or the S-oxides. Examples and suitable values of the term "heterocyclic group" are morpholino, piperidyl, pyridyl, pyranyl, pyrrolyl, isothiazolyl, indolyl, quinolyl, thienyl, 1,3-benzodioxolyl, thiadiazolyl, piperazinyl, thiazolidinyl, pyrrolidinyl, thiomorpholino, pyrrolinyl, homopiperazinyl, 3,5-dioxapiperidinyl, tetrahydropyranyl, imidazolyl, pyrimidyl, pyrazinyl, pyridazinyl,

isoxazolyl, *N*-methylpyrrolyl, 4-pyridone, 1-isoquinolone, 2-pyrrolidone, 4-thiazolidone, pyridine-*N*-oxide and quinoline-*N*-oxide. Preferably a "heterocyclic group" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a $-CH_2-$ group can optionally be replaced by a -C(O)-, a ring nitrogen atom may optionally bear a C_{1-6}alkyl group and form a quaternary compound or a ring nitrogen and/or sulphur atom may be optionally oxidised to form the *N*-oxide and or the S-oxides.

A suitable value for phenyl fused to a C_{5-7}cycloalkyl ring is indanyl or tetralinyl.

An example of "C_{1-6}alkanoyloxy" is acetoxy. Examples of "C_{1-6}alkoxycarbonyl" include C_{1-4}alkoxycarbonyl, methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C_{1-6}alkoxy" include C_{1-3}alkoxy, methoxy, ethoxy and propoxy. Examples of "C_{1-6}alkanoylamino" include C_{1-3}alkanoylamino, formamido, acetamido and propionylamino. Examples of "C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2" include C_{1-4}alkylsulphonyl, C_{1-3}alkyl$S(O)_a$, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of "C_{1-6}alkanoyl" include C_{1-4}alkanoyl, C_{1-3}alkanoyl, propionyl and acetyl. Examples of "*N*-C_{1-6}alkylamino" include *N*-(C_{1-3}alkyl)amino, methylamino and ethylamino. Examples of "*N,N*-(C_{1-6}alkyl)$_2$amino" include *N,N*-(C_{1-2}alkyl)$_2$amino, di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of "C_{2-6}alkenyl" are C_{2-3}alkenyl, vinyl, allyl and 1-propenyl. Examples of "C_{2-6}alkynyl" are C_{2-3}alkynyl, ethynyl, 1-propynyl and 2-propynyl. Examples of "*N*-(C_{1-6}alkyl)sulphamoyl" are *N*-(C_{1-3}alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)$_2$sulphamoyl" are *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl, *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N*-(C_{1-6}alkyl)carbamoyl" are *N*-(C_{1-4}alkyl)carbamoyl, *N*-(C_{1-3}alkyl)carbamoyl, methylaminocarbonyl and ethylaminocarbonyl. Examples of "*N,N*-(C_{1-6}alkyl)$_2$carbamoyl" are *N,N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C_{5-7}cycloalkyl ring" are cyclopropyl and cyclohexyl. Examples of "(heterocyclic group)C_{1-6}alkyl" include pyridylmethyl, 3-morpholinopropyl and 2-pyrimid-2-ylethyl. Examples of "(heterocyclic group)thio" include thienylthio and pyridylthio. Examples of "C_{3-8}cycloalkyl" include cyclopropyl and cyclohexyl. Examples of "C_{3-8}cycloalkylC_{1-6}cycloalkyl" include cyclopropylmethyl and 2-cyclohexylpropyl. Examples of "C_{1-6}alkoxycarbonylamino" include methoxycarbonylamino and *t*-butoxycarbonylamino.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the formula (I) may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the formula (I). Examples of pro-drugs include *in vivo* hydrolysable esters of a compound of the formula (I).

An *in vivo* hydrolysable ester of a compound of the formula (I) containing carboxy or hydroxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid or alcohol. Suitable pharmaceutically acceptable esters for carboxy include C_{1-6}alkoxymethyl esters for example methoxymethyl, C_{1-6}alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, C_{3-8}cycloalkoxycarbonyloxyC_{1-6}alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and C_{1-6}alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

An *in vivo* hydrolysable ester of a compound of the formula (I) containing a hydroxy group includes inorganic esters such as phosphate esters and α-acyloxyalkyl ethers and related compounds which as a result of the *in vivo* hydrolysis of the ester breakdown to give the parent hydroxy group. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxy-methoxy. A selection of *in vivo* hydrolysable ester forming groups for hydroxy include alkanoyl, benzoyl, phenylacetyl and substituted benzoyl and phenylacetyl, alkoxycarbonyl (to give alkyl carbonate esters), dialkylcarbamoyl and *N*-(dialkylaminoethyl)-*N*-alkylcarbamoyl (to give carbamates), dialkylaminoacetyl and carboxyacetyl. Examples of substituents on benzoyl include morpholino and piperazino linked from a ring nitrogen atom via a methylene group to the 3- or 4- position of the benzoyl ring.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention encompasses all such optical, diastereoisomers and geometric isomers that possess CDK inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess CDK inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess CDK inhibitory activity.

In another aspect of the invention, there is provided a compound of formula (I) (as depicted above) wherein:

Ring A is imidazo[1,2a]pyrid-3-yl or pyrazolo[2,3a]pyrid-3-yl;

$\mathbf{R^2}$ is attached to a ring carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl;

m is 0-5; wherein the values of R^2 may be the same or different;

$\mathbf{R^1}$ is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-2}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl;

n is 0 to 2, wherein the values of R^1 may be the same or different;

Ring B is phenyl or phenyl fused to a C_{5-7}cycloalkyl ring;

$\mathbf{R^3}$ is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^3 may be the same or different;

$\mathbf{R^4}$ is a group A-E-; wherein

A is optionally substituted on carbon by one or more D and is selected from C_{1-6}alkyl, phenyl, a heterocyclic group, phenylC_{1-6}alkyl or (heterocyclic group)C_{1-6}alkyl;

E is a direct bond or -O-, -C(O)-, -OC(O)-, -C(O)O-, -N(R^a)C(O)-, -C(O)N(R^a)-, -N(R^a)-, -S(O)$_r$-, -SO_2N(R^a)- or -N(R^a)SO_2-; wherein R^a is hydrogen or C_{1-6}alkyl optionally substituted by one or more D and r is 0-2;

D is independently selected from oxo, halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; and

q is 0-2; wherein the values of R^4 maybe the same or different; and wherein $p + q \leq 5$; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred values of R^1, R^2, R^3, R^4, n, m, p, q, Ring A and Ring B are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or hereinafter.

In one aspect of the invention preferably Ring A is imidazo[1,2a]pyrid-3-yl.

In another aspect of the invention preferably Ring A is pyrazolo[2,3a]pyrid-3-yl.

Preferably R^2 is attached to a ring carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, C_{1-3}alkanoyloxy, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-2}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl and *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl.

More preferably R^2 is attached to a ring carbon and is C_{1-3}alkyl.

Particularly R^2 is attached to a ring carbon and is methyl.

In another aspect of the invention, preferably R^2 is attached to a ring carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, C_{1-3}alkanoyloxy, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-3}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-3}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-3}alkoxycarbonyl, *N*-(C_{1-3}alkyl)sulphamoyl, *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl, phenyl, heterocyclic group, phenylthio or (heterocyclic group)thio; wherein any C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, phenyl or heterocyclic group may be optionally substituted on carbon

by one or more G; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q.

In another aspect of the invention, more preferably R^2 is attached to a ring carbon and is selected from halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkyl$S(O)_a$ wherein a is 0, phenyl, phenylthio or (heterocyclic group)thio; wherein any C_{1-6}alkyl, phenyl or heterocyclic group may be optionally substituted on carbon by one or more G; wherein G is selected from hydroxy and dimethylamino.

In another aspect of the invention, particularly R^2 is attached to a ring carbon and is selected from bromo, cyano, methyl, methoxy, ethylthio, 2-hydroxyethylthio, 2-dimethylaminoethylthio, phenyl, phenylthio or thien-2-ylthio.

In another aspect of the invention, more particularly R^2 is attached to a ring carbon and is selected from bromo, cyano, methyl, methoxy, ethylthio, 2-hydroxyethylthio or 2-dimethylaminoethylthio.

In another aspect of the invention, particularly preferred R^2 is attached to a ring carbon and is selected from 2-hydroxyethylthio.

In a further aspect of the invention, preferably R^2 is attached to a ring carbon and is selected from fluoro, chloro, bromo, cyano, methyl, methoxy, ethylthio, 2-hydroxyethylthio or 2-dimethylaminoethylthio.

Preferably m is 0-2; wherein the values of R^2 may be the same or different.

In one aspect of the invention preferably m is 0.

In another aspect of the invention preferably m is 1.

In a further aspect of the invention preferably m is 2; wherein the values of R^2 may be the same or different.

In a further aspect of the invention, preferably R^2 is attached to a ring carbon and is selected from fluoro, chloro, bromo, cyano, methyl, methoxy, ethylthio, 2-hydroxyethylthio or 2-dimethylaminoethylthiom and m is 0-2; wherein the values of R^2 may be the same or different.

Preferably R^2 is attached to a ring carbon and is selected from bromo, cyano, methyl, methoxy, ethylthio, 2-hydroxyethylthio or 2-dimethylaminoethylthio and m is 0-2; wherein the values of R^2 may be the same or different.

Preferably Ring A and $(R^2)_m$ together form imidazo[1,2a]pyrid-3-yl, pyrazolo[2,3a]pyrid-3-yl, 2-methylimidazo[1,2a]pyrid-3-yl, 2-methylpyrazolo[2,3a]pyrid-3-yl or 2,5-dimethylimidazo[1,2a]pyrid-3-yl.

In another aspect of the invention preferably Ring A and $(R^2)_m$ together form imidazo[1,2a]pyrid-3-yl, pyrazolo[2,3a]pyrid-3-yl, 2-methylimidazo[1,2a]pyrid-3-yl, 2-methylpyrazolo[2,3a]pyrid-3-yl, 2,5-dimethylimidazo[1,2a]pyrid-3-yl, 6-phenylimidazo[1,2a]pyrid-3-yl, 2-methyl-6-methoxyimidazo[1,2a]pyrid-3-yl, 5-bromoimidazo[1,2a]pyrid-3-yl, 5-phenylthioimidazo[1,2a]pyrid-3-yl, 5-ethylthioimidazo[1,2a]pyrid-3-yl, 5-(2-hydroxyethylthio)imidazo[1,2a]pyrid-3-yl, 5-thien-2-ylthioimidazo[1,2a]pyrid-3-yl, 5-cyanoimidazo[1,2a]pyrid-3-yl or 5-(2-dimethylaminoethylthio)imidazo[1,2a]pyrid-3-yl.

In another aspect of the invention more preferably Ring A and $(R^2)_m$ together form imidazo[1,2a]pyrid-3-yl or 5-(2-hydroxyethylthio)imidazo[1,2a]pyrid-3-yl.

Preferably n is 0 or 1 and where n is 1 preferably R^1 is attached to the 5-position of the pyrimidine ring.

More preferably n is 0.

Preferably R^1 is halo or C_{1-3}alkylS(O)$_a$ wherein a is 0; wherein the C_{1-3}alkyl group may be optionally substituted on carbon by one or more J; wherein J is hydroxy.

More preferably R^1 is bromo or 2-hydroxyethylthio.

Particularly R^1 is bromo or 2-hydroxyethylthio and n is 0-1.

Preferably Ring B is phenyl or indanyl.

More preferably Ring B is phenyl or indan-5-yl.

Particularly Ring B is phenyl.

Preferably R^3 is halo or sulphamoyl.

More preferably R^3 is fluoro, chloro, bromo or sulphamoyl.

Particularly R^3 is chloro or sulphamoyl.

More particularly R^3 is sulphamoyl.

Preferably p is 0-2; wherein the values of R^3 may be the same or different.

In one aspect of the invention preferably p is 0.

In another aspect of the invention preferably p is 1.

In a further aspect of the invention preferably p is 2; wherein the values of R^3 may be the same or different.

Preferably R^3 is fluoro, chloro, bromo or sulphamoyl; and p is 1.

In a further aspect of the invention when Ring B is phenyl and p is 1, preferably R^3 is attached meta to the -NH- moiety of formula (I).

Preferably R^a is hydrogen.

Preferably E is $-NHSO_2-$.

Preferably R^4 is a group A-E-; wherein

A is optionally substituted on carbon by one or more D and is selected from C_{1-4}alkyl, phenyl, a heterocyclic group or phenylC_{1-4}alkyl;

E is a direct bond or -O-, -C(O)-, $-N(R^a)C(O)-$, $-S(O)_r-$ or $-N(R^a)SO_2-$; wherein R^a is hydrogen, methyl or ethyl and r is 0-2;

D is oxo, cyano, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-2}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, C_{1-3}alkyl$S(O)_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl.

More preferably R^4 is a group A-E-; wherein

A is optionally substituted on carbon by one or more D and is selected from C_{1-4}alkyl, phenyl, a heterocyclic group or phenylC_{1-4}alkyl;

E is a direct bond or -O-, -C(O)- or $-S(O)_r-$; wherein r is 0-2;

D is hydroxy or *N,N*-(C_{1-2}alkyl)$_2$amino.

Particularly R^4 is methyl, ethyl, methoxy, methylthio, mesyl, acetyl, 3-*N,N*-dimethylamino-2-hydroxypropoxy, 2-*N,N*-diethylaminoethoxy, benzyloxy, anilinosulphonyl, pyrimidin-2-ylaminosulphonyl, phenoxy, 3,5-dioxapiperidin-1-ylsulphonyl.

In another aspect of the invention, preferably R^4 is a group A-E-; wherein

A is selected from C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl; which C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

E is a direct bond or -O-, -C(O)-, $-N(R^a)C(O)-$, $-S(O)_r-$ or $-N(R^a)SO_2-$; wherein R^a is hydrogen or C_{1-6}alkyl and r is 0-2;

D is independently selected from hydroxy, amino, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonylamino or benzyloxycarbonylamino; wherein any C_{1-6}alkyl may be optionally substituted on carbon by one or more K;

K is selected from hydroxy or diethylamino; and

R is C_{1-4}alkyl.

In another aspect of the invention, more preferably R^4 is a group A-E-; wherein

A is selected from methyl, ethyl, propyl, pentyl, phenyl, pyrimidyl, 3,5-dioxapiperidin-1-yl, cyclopropyl, benzyl, pyrrolidin-1-ylethyl, piperidin-1-ylethyl, pyrrolidin-2-ylethyl, 3-(2-oxo-pyrrolidin-1-yl)propyl, 3-imidazol-1-ylpropyl, 2-morpholinoethyl, 3-morpholinopropyl, 2-imidazol-4-ylethyl, 2-piperazin-1-ylethyl, 3-piperazin-1-ylpropyl or cyclopropylmethyl; wherein A may be optionally substituted on carbon by one or more D; and wherein pyrrolidin-2-yl, imidazol-4-yl or piperazin-1-yl may be optionally substituted on nitrogen by a group selected from R;

E is a direct bond or -O-, -C(O)-, -N(R^a)C(O)-, -S(O)$_r$- or -N(R^a)SO_2-; wherein R^a is hydrogen or methyl and r is 0-2;

D is independently selected from hydroxy, amino, methoxy, methylamino, ethylamino, isopropylamino, *N,N*-dimethylamino, *N,N*-diethylamino, *t*-butoxycarbonylamino or benzyloxycarbonylamino; wherein any methyl, ethyl, isopropyl or *t*-butyl may be optionally substituted on carbon by one or more K;

K is selected from hydroxy or diethylamino; and

R is methyl.

In another aspect of the invention, particularly R^4 is methyl, ethyl, methoxy, methylthio, acetyl, benzyloxy, mesyl, *N,N*-diethylaminoethoxy, 3-*N,N*-dimethylamino-2-hydroxypropoxy, phenoxy, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, *N*-(3-imidazol-1-ylpropyl)carbamoyl, *N*-[3-(2-oxo-pyrrolidin-1-yl)propyl]carbamoyl, 3,5-dioxapiperidin-1-ylsulphonyl, *N*-cyclopropylsulphamoyl, *N*-cyclopropylmethylsulphamoyl, anilinosulphonyl, *N*-pyrimidin-2-ylsulphamoyl, *N*-methylsulphamoyl, *N*-propylsulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-methylaminoethyl)sulphamoyl, *N*-(2-isopropylaminoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-(2-diethylaminoethyl)sulphamoyl, *N*-[2-(hydroxyethylamino)ethyl]sulphamoyl, *N*-[2-(diethylaminoethyl)ethyl]sulphamoyl, *N*-(pyrrolidin-1-ylethyl)sulphamoyl, *N*-[2-(1-methylpyrrolidin-2-yl)ethyl]sulphamoyl, *N*-(2-piperidin-1-ylethyl)sulphamoyl, *N*-(2-piperazin-1-ylethyl)sulphamoyl, *N*-(2-morpholinoethyl)sulphamoyl, *N*-(2-imidazol-4-ylethyl)sulphamoyl, *N*-(3-hydroxypropyl)sulphamoyl, *N*-(2,3-dihydroxypropyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-aminopropyl)sulphamoyl, *N*-(3-methylaminopropyl)sulphamoyl,

N-(3-dimethylaminopropyl)sulphamoyl, *N*-(3-diethylaminopropyl)sulphamoyl, *N*-(3-isopropylaminopropyl)sulphamoyl, *N*-(3-*t*-butoxycarbonylaminopropyl)sulphamoyl, *N*-(3-benzyloxycarbonylaminopropyl)sulphamoyl, *N*-[3-(2-oxopyrrolidin-1-yl)propyl]sulphamoyl, *N*-(3-morpholinopropyl)sulphamoyl, *N*-[3-(4-methylpiperazin-1-yl)propyl]sulphamoyl, *N*-(3-imidazol-1-ylpropyl)sulphamoyl or *N*-(5-hydroxypentyl)sulphamoyl.

In another aspect of the invention, more particularly R^4 is *N*-methylsulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-methylaminoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-dimethylaminopropyl)sulphamoyl or *N*-(3-isopropylaminopropyl)sulphamoyl.

Preferably R^4 is methyl, ethyl, methoxy, methylthio, acetyl, benzyloxy, mesyl, *N,N*-diethylaminoethoxy, 3-*N,N*-dimethylamino-2-hydroxypropoxy, phenoxy, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, *N*-(3-imidazol-1-ylpropyl)carbamoyl, *N*-[3-(2-oxo-pyrrolidin-1-yl)propyl]carbamoyl, 3,5-dioxapiperidin-1-ylsulphonyl, *N*-cyclopropylsulphamoyl, *N*-cyclopropylmethylsulphamoyl, anilinosulphonyl, *N*-pyrimidin-2-ylsulphamoyl, *N*-methylsulphamoyl, *N*-propylsulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-methylaminoethyl)sulphamoyl, *N*-(2-isopropylaminoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-(2-diethylaminoethyl)sulphamoyl, *N*-[2-(hydroxyethylamino)ethyl]sulphamoyl, *N*-[2-(diethylaminoethyl)ethyl]sulphamoyl, *N*-(pyrrolidin-1-ylethyl)sulphamoyl, *N*-[2-(1-methylpyrrolidin-2-yl)ethyl]sulphamoyl, *N*-(2-piperidin-1-ylethyl)sulphamoyl, *N*-(2-piperazin-1-ylethyl)sulphamoyl, *N*-(2-morpholinoethyl)sulphamoyl, *N*-(2-imidazol-4-ylethyl)sulphamoyl, *N*-(3-hydroxypropyl)sulphamoyl, *N*-(2,3-dihydroxypropyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-aminopropyl)sulphamoyl, *N*-(3-methylaminopropyl)sulphamoyl, *N*-(3-dimethylaminopropyl)sulphamoyl, *N*-(3-diethylaminopropyl)sulphamoyl, *N*-(3-isopropylaminopropyl)sulphamoyl, *N*-(3-*t*-butoxycarbonylaminopropyl)sulphamoyl, *N*-(3-benzyloxycarbonylaminopropyl)sulphamoyl, *N*-[3-(2-oxopyrrolidin-1-yl)propyl]sulphamoyl, *N*-(3-morpholinopropyl)sulphamoyl, *N*-[3-(4-methylpiperazin-1-yl)propyl]sulphamoyl, *N*-(3-imidazol-1-ylpropyl)sulphamoyl or *N*-(5-hydroxypentyl)sulphamoyl; and q is 1.

Preferably q is 0-1.

In one aspect of the invention q is 0.

In another aspect of the invention q is 1.

In a further aspect of the invention when Ring B is phenyl and q is 1, preferably R^4 is attached para to the -NH- moiety of formula (I).

Preferably Ring B, $(R^3)_p$ $(R^4)_q$ and together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 3-methylphenyl, 4-methylphenyl, 3-ethylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-methylthiophenyl, 4-methylthiophenyl, 4-mesylphenyl, 3-sulphamoylphenyl, 4-sulphamoylphenyl, 3-acetylphenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-4-methylphenyl, 4-(3-*N,N*-dimethylamino-2-hydroxypropoxy)phenyl, 4-benzyloxyphenyl, 4-anilinosulphonylphenyl, 4-(pyrimidin-2-ylsulphonyl)phenyl, 4-phenoxyphenyl, 4-(2-*N,N*-diethylaminoethoxy)phenyl, 4-(3,5-dioxapiperidin-1-ylsulphonyl)phenyl or indanyl.

In another aspect of the invention, more preferably Ring B, $(R^3)_p$ $(R^4)_q$ and together form phenyl, 2-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 3-chlorophenyl, 3-bromophenyl, 3-methylphenyl, 3-methoxyphenyl, 3-methylthiophenyl, 3-acetylphenyl, 3-ethylphenyl, 3-sulphamoylphenyl, 4-fluorophenyl, 4-chlorophenyl, 4-methylphenyl, 4-methoxyphenyl, 4-sulphamoylphenyl, 3-methyl 4-sulphamoylphenyl, 4-(*N*-methylcarbamoyl)phenyl, 4-(*N,N*-dimethylcarbamoyl)phenyl, 4-methylthiophenyl, 4-mesylphenyl, 4-(*N*-methylsulphamoyl)phenyl, 4-(*N*-propylsulphamoyl)phenyl, 3-chloro-4-(*N*-propylsulphamoyl)phenyl, 4-(*N,N*-diethylaminoethoxy)phenyl, 4-benzyloxyphenyl, 4-phenoxyphenyl, 4-(*N*-cyclopropylsulphamoyl)phenyl, 4-(*N*-cyclopropylmethylsulphamoyl)phenyl, 4-(3,5-dioxapiperidin-1-ylsulphonyl)phenyl, 4-anilinosulphonylphenyl, 4-(*N*-pyrimidin-2-ylsulphamoyl)phenyl, 4-[*N*-(2-methoxyethyl)sulphamoyl]phenyl, 3-chloro-4-[*N*-(2-methoxyethyl)sulphamoyl]phenyl, 3-methyl-4-[*N*-(2-methoxyethyl)sulphamoyl]phenyl, 4-[*N*-(3-diethylaminopropyl)sulphamoyl]phenyl, 4-{*N*-[2-(1-methylpyrrolidin-2-yl)ethyl]sulphamoyl]}phenyl, 3-chloro-4-fluorophenyl, 3,4-dichlorophenyl, 2-chloro-4-methylphenyl, 4-(3-*N,N*-dimethylamino-2-hydroxypropoxy)phenyl, 4-[*N*-(3-hydroxypropyl)sulphamoyl]phenyl,

4-{*N*-[3-(2-oxopyrrolidin-1-yl)propyl]sulphamoyl}phenyl,
4-[*N*-(5-hydroxypentyl)sulphamoyl]phenyl, 4-[*N*-(3-methoxypropyl)sulphamoyl]phenyl,
indan-5-ylamino, 4-[*N*-(3-isopropylaminopropyl)sulphamoyl]phenyl,
4-[*N*-(2-isopropylaminoethyl)sulphamoyl]phenyl,
4-[*N*-(3-imidazol-1-ylpropyl)sulphamoyl]phenyl,
4-[*N*-(3-dimethylaminopropyl)sulphamoyl]phenyl,
4-[*N*-(3-morpholinopropyl)sulphamoyl]phenyl,
3-methyl-4-[*N*-(3-morpholinopropyl)sulphamoyl]phenyl,
4-[*N*-(3-aminopropyl)sulphamoyl]phenyl,
4-{*N*-[2-(hydroxyethylamino)ethyl]sulphamoyl}phenyl,
4-[*N*-(2-imidazol-4-ylethyl)sulphamoyl]phenyl,
4-[*N*-(3-methylaminopropyl)sulphamoyl]phenyl,
4-[*N*-(2-piperazin-1-ylethyl)sulphamoyl]phenyl,
4-[*N*-[3-(4-methylpiperazin-1-yl)propyl]sulphamoyl]phenyl,
4-[*N*-(2,3-dihydroxypropyl)sulphamoyl]phenyl,
4-[*N*-(3-imidazol-1-ylpropyl)carbamoyl]phenyl,
4-[*N*-[2-(diethylaminoethyl)ethyl]sulphamoyl]phenyl,
4-[*N*-[3-(2-oxo-pyrrolidin-1-yl)propyl]carbamoyl]phenyl,
4-[*N*-(2-dimethylaminoethyl)sulphamoyl]phenyl,
4-[*N*-(2-morpholinoethyl)sulphamoyl]phenyl,
3-methyl-4-[*N*-(2-morpholinoethyl)sulphamoyl]phenyl,
4-[*N*-(pyrrolidin-1-ylethyl)sulphamoyl]phenyl, 4-[*N*-(2-methylaminoethyl)sulphamoyl]phenyl,
4-[*N*-(2-piperidin-1-ylethyl)sulphamoyl]phenyl,
4-[*N*-(2-diethylaminoethyl)sulphamoyl]phenyl,
4-[*N*-(3-*t*-butoxycarbonylaminopropyl)sulphamoyl]phenyl,
4-[*N*-(3-benzyloxycarbonylaminopropyl)sulphamoyl]phenyl or
4-[*N*-(3-diethylaminopropyl)sulphamoyl]phenyl.

In another aspect of the invention, particularly Ring B, $(R^3)_p$ $(R^4)_q$ and together form
4-sulphamoylphenyl, 4-(*N*-methylsulphamoyl)phenyl,
4-[*N*-(2-methoxyethyl)sulphamoyl]phenyl, 4-[*N*-(3-methoxypropyl)sulphamoyl]phenyl,
4-[*N*-(3-isopropylaminopropyl)sulphamoyl]phenyl,
4-[*N*-(3-dimethylaminopropyl)sulphamoyl]phenyl,
4-[*N*-(2-dimethylaminoethyl)sulphamoyl]phenyl or

4-[*N*-(2-methylaminoethyl)sulphamoyl]phenyl

Therefore in one aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

Ring A is imidazo[1,2a]pyrid-3-yl or pyrazolo[2,3a]pyrid-3-yl;

R^2 is attached to a ring carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, C_{1-3}alkanoyloxy, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-2}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl and *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl;

m is 0-2; wherein the values of R^2 may be the same or different;

n is 0;

Ring B is phenyl or indanyl;

R^3 is halo or sulphamoyl;

R^4 is a group A-E-; wherein

A is optionally substituted on carbon by one or more D and is selected from C_{1-4}alkyl, phenyl, a heterocyclic group or phenylC_{1-4}alkyl;

E is a direct bond or -O-, -C(O)-, -N(R^a)C(O)-, -S(O)$_r$- or -N(R^a)SO_2-; wherein R^a is hydrogen, methyl or ethyl and r is 0-2;

p is 0-2; wherein the values of R^3 may be the same or different;

D is oxo, cyano, hydroxy, amino, carboxy, carbamoyl, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-2}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl;

q is 0-1; wherein the values of R^4 may be the same or different;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

Ring A is imidazo[1,2a]pyrid-3-yl or pyrazolo[2,3a]pyrid-3-yl;

R^2 is attached to a ring carbon and is C_{1-3}alkyl;

m is 0-2; wherein the values of R^2 may be the same or different;

n is 0;

Ring B is phenyl or indan-5-yl;

R^3 is fluoro, chloro, bromo or sulphamoyl;

p is 0-2; wherein the values of R^3 may be the same or different;

R^4 is methyl, ethyl, methoxy, methylthio, mesyl, acetyl,

3-*N,N*-dimethylamino-2-hydroxypropoxy, 2-*N,N*-diethylaminoethoxy, benzyloxy, anilinosulphonyl, pyrimidin-2-ylaminosulphonyl, phenoxy, 3,5-dioxapiperidin-1-ylsulphonyl.

q is 0-1; wherein the values of R^4 may be the same or different;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in an additional aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

Ring A and $(R^2)_m$ together form imidazo[1,2a]pyrid-3-yl, pyrazolo[2,3a]pyrid-3-yl, 2-methylimidazo[1,2a]pyrid-3-yl, 2-methylpyrazolo[2,3a]pyrid-3-yl or 2,5-dimethylimidazo[1,2a]pyrid-3-yl;

n is 0;

Ring B, $(R^3)_p$ and $(R^4)_q$ together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 3-methylphenyl, 4-methylphenyl, 3-ethylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-methylthiophenyl, 4-methylthiophenyl, 4-mesylphenyl, 3-sulphamoylphenyl, 4-sulphamoylphenyl, 3-acetylphenyl, 3,4-dichlorophenyl, 3-chloro-4-fluorophenyl, 2-chloro-4-methylphenyl, 4-(3-*N,N*-dimethylamino-2-hydroxypropoxy)phenyl, 4-benzyloxyphenyl, 4-anilinosulphonylphenyl, 4-(pyrimidin-2-ylsulphonyl)phenyl, 4-phenoxyphenyl, 4-(2-*N,N*-diethylaminoethoxy)phenyl, 4-(3,5-dioxapiperidin-1-ylsulphonyl)phenyl or indanyl; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a further additional aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

Ring A is imidazo[1,2a]pyrid-3-yl or pyrazolo[2,3a]pyrid-3-yl;

R^1 is halo or C_{1-3}alkylS(O)$_a$ wherein a is 0; wherein the C_{1-3}alkyl group may be optionally substituted on carbon by one or more J; wherein J is hydroxy.

n is 0-1;

R^2 is attached to a ring carbon and is selected from halo, cyano, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylS(O)$_a$ wherein a is 0, phenyl, phenylthio or (heterocyclic group)thio; wherein any

C_{1-6}alkyl, phenyl or heterocyclic group may be optionally substituted on carbon by one or more G; wherein G is selected from hydroxy and dimethylamino.

m is 0-2; wherein the values of R^2 may be the same or different;

Ring B is phenyl or indan-5-yl;

R^3 is fluoro, chloro, bromo or sulphamoyl;

p is 0-1;

R^4 is a group A-E-; wherein

A is selected from C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl; which C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

E is a direct bond or -O-, -C(O)-, -N(R^a)C(O)-, -S(O)$_r$- or -N(R^a)SO_2-; wherein R^a is hydrogen or C_{1-6}alkyl and r is 0-2;

D is independently selected from hydroxy, amino, C_{1-6}alkoxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkoxycarbonylamino or benzyloxycarbonylamino; wherein any C_{1-6}alkyl may be optionally substituted on carbon by one or more K;

K is selected from hydroxy or diethylamino; and

R is C_{1-4}alkyl; and

q is 0-1;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Therefore in a another additional aspect of the invention, there is provided a compound of formula (I) as depicted above wherein:

Ring A is imidazo[1,2a]pyrid-3-yl;

n is 0;

Ring B is phenyl;

R^3 is sulphamoyl;

p is 0-1;

R^4 is *N*-methylsulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-methylaminoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-dimethylaminopropyl)sulphamoyl or *N*-(3-isopropylaminopropyl)sulphamoyl; and

q is 0-1;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In another aspect of the invention, preferred compounds of the invention are any one of Examples 1-38 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

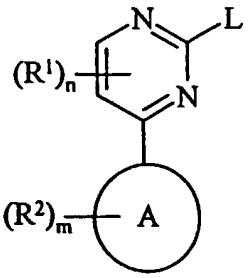
In another aspect of the invention, preferred compounds of the invention are any one of Examples 1-98 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

In a further aspect of the invention, preferred compounds of the invention are Examples 7, 39, 40, 52, 53, 55, 65, 68 and 86 or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

Preferred aspects of the invention are those which relate to the compound of formula (I) or a pharmaceutically acceptable salt thereof.

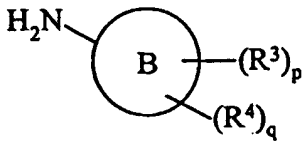
Another aspect of the present invention provides a process for preparing a compound of formula (I) or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof which process (wherein R^1, R^2, R^3, R^4, Ring A, Ring B, m, p, q and n are, unless otherwise specified, as defined in formula (I)) comprises of:

a) reaction of a pyrimidine of formula (II):



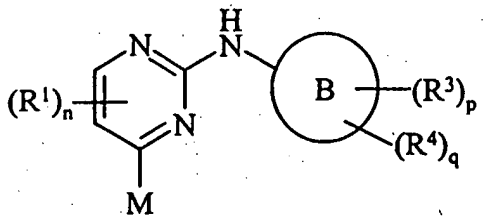
(II)

wherein L is a displaceable group; with an amine of formula (III):



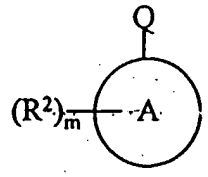
(III)

b) reacting a pyrimidine of formula (IV):



(IV)

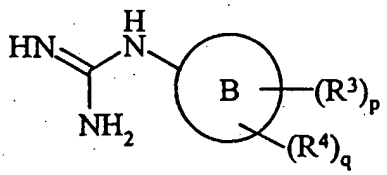
with a compound of the formula (V):



(V)

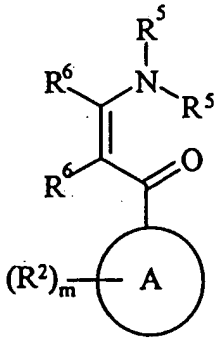
wherein one of M and Q is a displaceable group X and the other is an metallic reagent Y; or

c) reacting a compounds of formula (VI):



(VI)

with a compound of formula (VII):



(VII)

wherein R^5 is C_{1-6}alkyl and R^6 is hydrogen or R^1;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

L is a displaceable group, suitable values for L are for example, a halogeno or sulphonyloxy group, for example a chloro, bromo, methanesulphonyloxy or toluene-4-sulphonyloxy group.

A suitable displaceable group X is, for example, a halogeno or sulphonyl group, for example a bromo, iodo or trifluoromethylsulphonyl group.

A suitable metallic group Y, is, for example, copper, lithium, an organoboron reagent such as $-B(OH)_2$, $-B(OPr^i)_2$ or $-B(Et)_2$, or an organotin compound such as $SnBu_3$, an organosilicon compound such as $Si(Me)F_2$, an organozirconium compound such as $ZrCl_3$, an organoaluminium compound such as $AlEt_2$, an organomagnesium compound such as MgBr, an organozinc compound such as ZnCl or an organomercury compound such as HgBr.

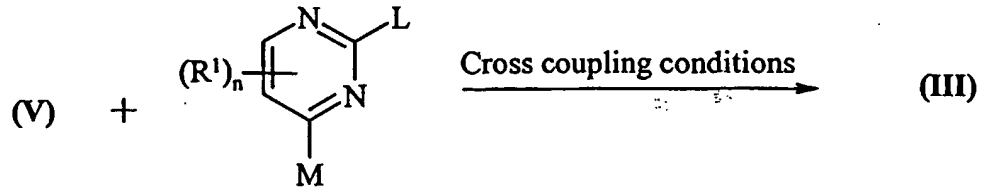
Specific reaction conditions for the above reactions are as follows.

a) Pyrimidines of formula **(II)** and amines of formula **(III)** may be reacted together:

i) in the presence of a suitable solvent for example a ketone such as acetone or an alcohol such as ethanol or butanol or an aromatic hydrocarbon such as toluene or *N*-methyl pyrrolidine, optionally in the presence of a suitable acid for example an inorganic acid such as hydrochloric acid or sulphuric acid, or an organic acid such as acetic acid or formic acid (or a suitable Lewis acid) and at a temperature in the range of 0°C to reflux, preferably reflux; or

ii) under standard Buchwald conditions (for example see *J. Am. Chem. Soc.*, **118**, 7215; *J. Am. Chem. Soc.*, **119**, 8451; *J. Org. Chem.*, **62**, 1568 and 6066) for example in the presence of palladium acetate, in a suitable solvent for example an aromatic solvent such as toluene, benzene or xylene, with a suitable base for example an inorganic base such as caesium carbonate or an organic base such as potassium-t-butoxide, in the presence of a suitable ligand such as 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl and at a temperature in the range of 25 to 80°C.

Pyrimidines of the formula **(II)** may be prepared according to SCHEME I



SCHEME I

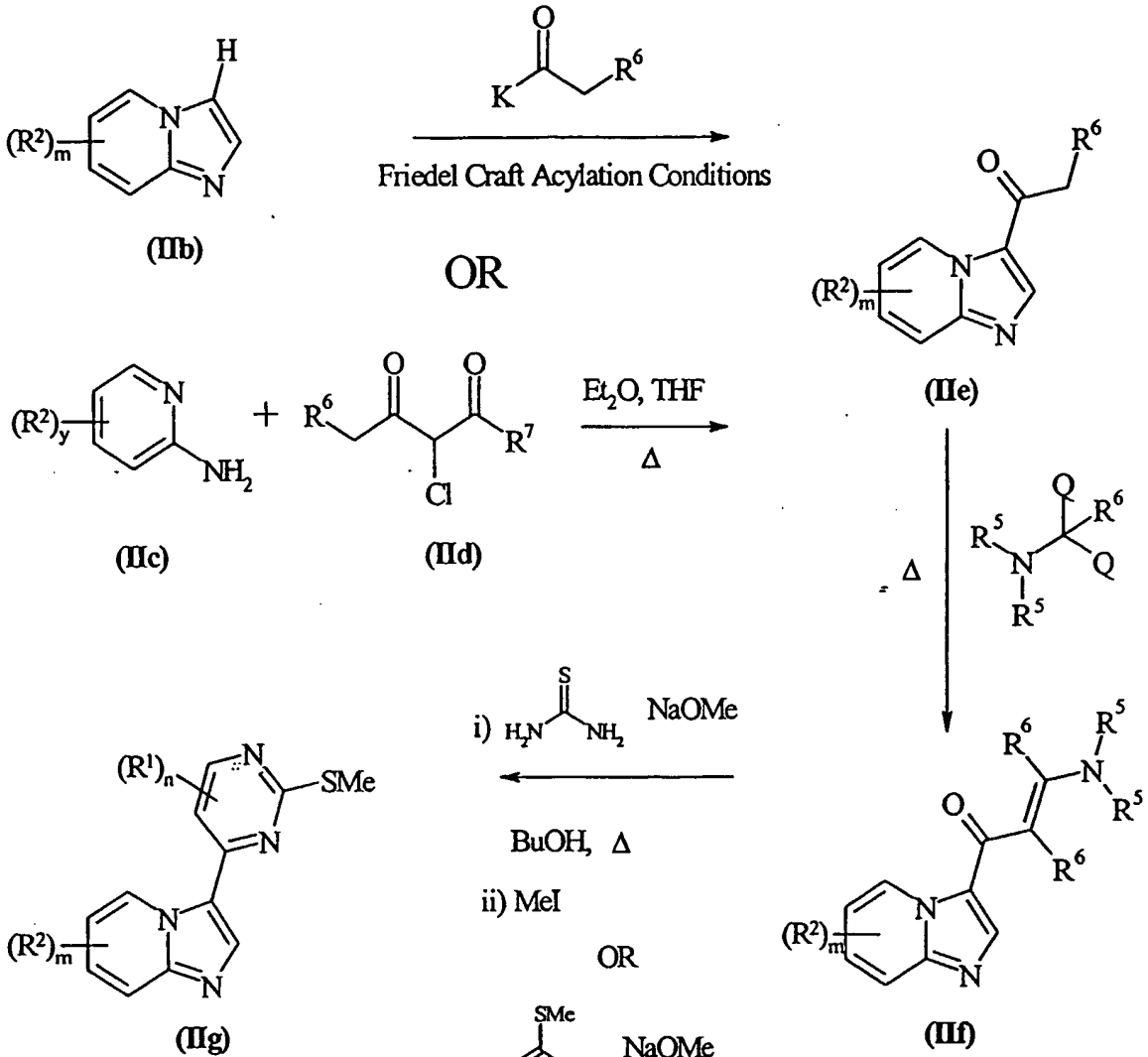
wherein one of M and Q is a displaceable group X as defined above and the other is an metallic reagent Y as defined above.

Cross coupling conditions are well known in the art. Suitable conditions include, for example, those described under b) below.

Where Ring A is imidazo[1,2a]pyrid-3-yl compounds of the formula **(II)** may also be prepared according to SCHEME II

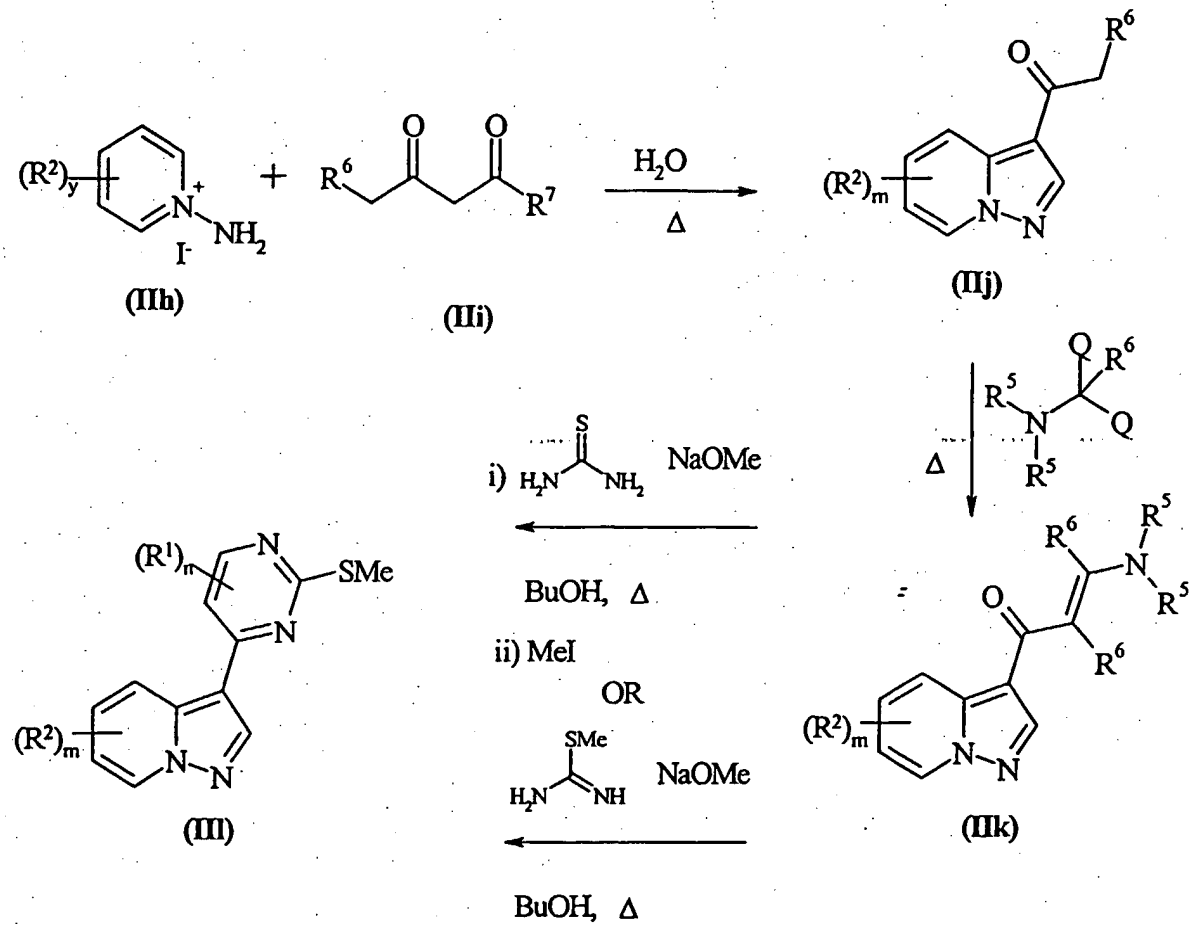
K is a suitable leaving group (for example C_{1-6}alkanoyloxy), R^6 is as defined above, y is 0-4, R^7 is hydrogen or R^2; Q is a suitable leaving group (for example C_{1-6}alkoxy) and R^5 is as defined above.

Where Ring A is pyrazolo[2,3a]pyrid-3-yl compounds of the formula **(II)** may also be prepared according to SCHEME III



(IIb) (IIc) (IId) (IIe) (IIf) (IIg)

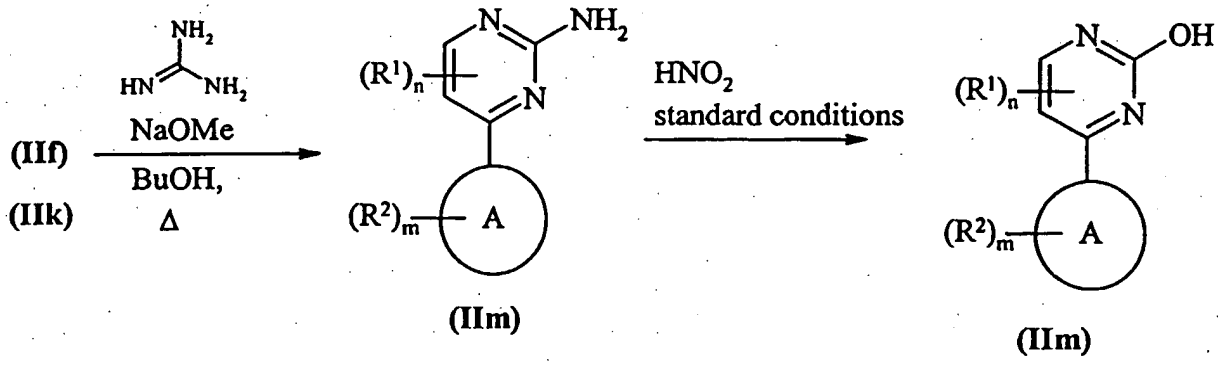
SCHEME II



SCHEME III

wherein R^5, R^6 and R^7 are as defined above.

Compounds of formula **(IIf)** or **(IIk)** may be further modified to produce compounds of formula **(IIn)**:



SCHEME IV

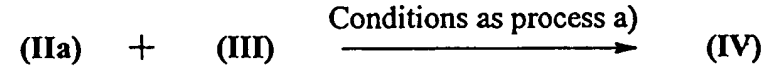
It will be appreciated by those skilled in the art that compounds of formula **(IIn)** may be additionally modified by standard functional group modification reactions known in the art

to produce compounds of formula (II) where L is other leaving groups for example chloro, bromo, tosyl and mesyl.

Compounds of formula (IIa), (IIb), (IIc), (IId), (IIh), (IIi) and (III) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

b) Compounds of formula (IV) and compounds of formula (V) may be reacted together under standard cross coupling conditions. Examples of these are in the presence of a catalyst, for example, a metallic catalyst such as tetrakis(triphenylphosphine)palladium(0), palladium(II) chloride, palladium(II) bromide, nickel(II) chloride, nickel(II) bromide or bis(triphenylphosphine)nickel(II) chloride, in the presence of a suitable inert solvent or diluent, for example tetrahydrofuran, 1,4-dioxan, 1,2-dimethoxyethane, benzene, toluene, xylene, methanol or ethanol. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium carbonate or potassium carbonate, pyridine, 4-dimethylaminopyridine, triethylamine or morpholine, and conveniently at a temperature in the range, for example 10 to 250°C, preferably in the range 60 to 120°C.

Compounds of formula (IV) may be prepared according to SCHEME V



SCHEME V

Compounds of formula (V) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art.

c) compounds of formula (VI) and compounds of formula (VII) are reacted together in a suitable solvent such as *N*-methylpyrrolidinone or butanol at a temperature in the range of 100-200°C, preferably in the range of 150-170°C. The reaction is preferably conducted in the presence of a suitable base such as, for example, sodium methoxide or potassium carbonate.

Compounds of formula (VI) and (VII) are commercially available compounds, or they are known in the literature, or they are prepared by standard processes known in the art, or compounds of formula (VII) may be prepared by a process similar to that described for (IIf) and (IIk) hereinabove.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately

following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis

acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possesses anti-cell-proliferation activity such as anti-cancer activity which is believed to arise from the CDK inhibitory activity of the compound. These properties may be assessed, for example, using the procedure set out below:-

Assay

The following abbreviations have been used :-

HEPES is *N*-[2-Hydroxyethyl]piperazine-*N*'-[2-ethanesulfonic acid]

DTT is Dithiothretiol

PMSF is Phenylmethylsulfonyl fluoride

The compounds were tested in an *in vitro* kinase assay in 96 well format using Scintillation Proximity Assay (SPA - obtained from Amersham) for measuring incorporation of [γ-33-P]-Adenosine Triphosphate into a test substrate (GST-Retinoblastoma protein; GST-Rb). In each well was placed the compound to be tested (diluted in DMSO and water to

correct concentrations) and in control wells either roscovitine as an inhibitor control or DMSO as a positive control.

Approximately 0.2µl of CDK2/Cyclin E partially-purified enzyme (amount dependent on enzyme activity) diluted in 25µl incubation buffer was added to each well then 20µl of GST-Rb/ATP/ATP33 mixture (containing 0.5µg GST-Rb and 0.2µM ATP and 0.14µCi [γ-33-P]-Adenosine Triphosphate in incubation buffer), and the resulting mixture shaken gently, then incubated at room temperature for 60 minutes.

To each well was then added 150µL stop solution containing (0.8mg/well of Protein A-PVT SPA bead (Amersham)), 20pM/well of Anti-Glutathione Transferase, Rabbit IgG (obtained from Molecular Probes), 61mM EDTA and 50mM HEPES pH 7.5 containing 0.05% sodium azide.

The plates were sealed with Topseal-S plate sealers, left for two hours then spun at 2500rpm, 1124xg., for 5 minutes. The plates were read on a Topcount for 30 seconds per well.

The incubation buffer used to dilute the enzyme and substrate mixes contained 50mM HEPES pH7.5, 10mM $MnCl_2$, 1mM DTT, 100µM Sodium vanadate, 100µM NaF, 10mM Sodium Glycerophosphate, BSA (1mg/ml final).

Test substrate

In this assay only part of the retinoblastoma protein (Science 1987 Mar13;235(4794):1394-1399; Lee W.H., Bookstein R., Hong F., Young L.J., Shew J.Y., Lee E.Y.) was used, fused to a GST tag. PCR of retinoblastoma gene encoding amino acids 379-928 (obtained from retinoblastoma plasmid ATCC pLRbRNL) was performed, and the sequence cloned into pGEX 2T fusion vector (Smith D.B. and Johnson, K.S. Gene 67, 31 (1988); which contained a tac promoter for inducible expression, internal lac I^q gene for use in any E.Coli host, and a coding region for thrombin cleavage - obtained from Pharmacia Biotech) which was used to amplify amino acids 792-928. This sequence was again cloned into pGEX 2T.

The retinoblastoma 792-928 sequence so obtained was expressed in E.Coli (BL21 (DE3) pLysS cells) using standard inducible expression techniques, and purified as follows.

E.coli paste was resuspended in 10ml/g of NETN buffer (50mM Tris pH 7.5, 120mM NaCl, 1mM EDTA, 0.5%v/v NP-40, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) and sonicated for 2 x 45 seconds per 100ml homogenate. After centrifugation, the supernatant was loaded onto a 10ml glutathione Sepharose column

(Pharmacia Biotech, Herts, UK), and washed with NETN buffer. After washing with kinase buffer (50mM HEPES pH 7.5, 10mM MgCl2, 1mM DTT, 1mM PMSF, 1ug/ml leupeptin, 1ug/ml aprotinin and 1ug/ml pepstatin) the protein was eluted with 50mM reduced glutathione in kinase buffer. Fractions containing GST-Rb(792-927) were pooled and dialysed overnight against kinase buffer. The final product was analysed by Sodium Dodeca Sulfate (SDS) PAGE (Polyacrylamide gel) using 8-16% Tris-Glycine gels (Novex, San Diego, USA).

CDK2 and Cyclin E

The open reading frames of CDK2 and Cyclin E were isolated by reverse transcriptase-PCR using HeLa cell and activated T cell mRNA as a template and cloned into the insect expression vector pVL1393 (obtained from Invitrogen 1995 catalogue number: V1392-20). CDK2 and cyclin E were then dually expressed [using a standard virus Baculogold co-infection technique] in the insect SF21 cell system (Spodoptera Frugiperda cells derived from ovarian tissue of the Fall Army Worm = commercially available).

Example production of Cyclin E/CDK2

The following Example provides details of the production of Cyclin E/CDK2 in SF21 cells (in TC100 + 10% FBS(TCS) + 0.2% Pluronic) having dual infection MOI 3 for each virus of Cyclin E & CDK2.

SF21 cells grown in a roller bottle culture to 2.33 x 10^6 cells/ml were used to inoculate 10 x 500 ml roller bottles at 0.2 x 10E6 cells/ml. The roller bottles were incubated on a roller rig at 28°C.

After 3 days (72 hrs.) the cells were counted, and the average from 2 bottles found to be 1.86 x 10E6 cells/ml. (99% viable). The cultures were then infected with the dual viruses at an MOI 3 for each virus.

The viruses were mixed together before addition to the cultures, and the cultures returned to the roller rig 28°C.

After 2 days (48 hrs.) post infection the 5 Litres of culture was harvested. The total cell count at harvest was 1.58 x 10E6 cells/ml.(99% viable). The cells were spun out at 2500rpm, 30 mins., 4°C in Heraeus Omnifuge 2.0 RS in 250 ml. lots. The supernatant was discarded.

Partial co-purification of Cdk2 and Cyclin E

Sf21 cells were resuspended in lysis buffer (50mM Tris pH 8.2, 10mM $MgCl_2$, 1mM DTT, 10mM glycerophosphate, 0.1mM sodium orthovanadate, 0.1mM NaF, 1mM PMSF,

1ug/ml leupeptin and 1ug/ml aprotinin) and homogenised for 2 minutes in a 10ml Dounce homgeniser. After centrifugation, the supernatant was loaded onto a Poros HQ/M 1.4/100 anion exchange column (PE Biosystems, Hertford, UK). Cdk2 and Cyclin E were coeluted at the beginning of a 0-1M NaCl gradient (run in lysis buffer minus protease inhibitors) over 20 column volumes. Co-elution was checked by western blot using both anti-Cdk2 and anti-Cyclin E antibodies (Santa Cruz Biotechnology, California, US).

By analogy, assays designed to assess inhibition of CDK4 and CDK6 may be constructed. CDK2 (EMBL Accession No. X62071) may be used together with Cyclin A or Cyclin E (see EMBL Accession No. M73812), and further details for such assays are contained in PCT International Publication No. WO99/21845, the relevant Biochemical & Biological Evaluation sections of which are hereby incorporated by reference.

Although the pharmacological properties of the compounds of the formula (I) vary with structural change, in general activity possessed by compounds of the formula (I) may be demonstrated at IC_{50} concentrations or doses in the range 250μM to 1nM.

When tested in the above in-vitro assay the CDK2 inhibitory activity of Example 11 was measured as $IC_{50} = 0.19\mu M$ and that of Example 12 as $IC_{50} = 0.17\mu M$.

The *in vivo* activity of the compounds of the present invention may be assessed by standard techniques, for example by measuring inhibition of cell growth and assessing cytotoxicity.

Inhibition of cell growth may be measured by staining cells with Sulforhodamine B (SRB), a fluorescent dye that stains proteins and therefore gives an estimation of amount of protein (i.e. cells) in a well (see Boyd, M.R.(1989) Status of the NCI preclinical antitumour drug discovery screen. Prin. Prac Oncol 10:1-12). Thus, the following details are provided of measuring inhibition of cell growth :-

Cells were plated in appropriate medium in a volume of 100ml in 96 well plates; media was Dulbecco's Modified Eagle media for MCF-7, SK-UT-1B and SK-UT-1. The cells were allowed to attach overnight, then inhibitor compounds were added at various concentrations in a maximum concentration of 1% DMSO (v/v). A control plate was assayed to give a value for cells before dosing. Cells were incubated at 37°C, (5% CO_2) for three days.

At the end of three days TCA was added to the plates to a final concentration of 16% (v/v). Plates were then incubated at 4°C for 1 hour, the supernatant removed and the plates washed in tap water. After drying, 100ml SRB dye (0.4% SRB in 1% acetic acid) was added

for 30 minutes at 37°C. Excess SRB was removed and the plates washed in 1% acetic acid. The SRB bound to protein was solubilised in 10mM Tris pH7.5 and shaken for 30 minutes at room temperature. The ODs were read at 540nm, and the concentration of inhibitor causing 50% inhibition of growth was determined from a semi-log plot of inhibitor concentration versus absorbance. The concentration of compound that reduced the optical density to below that obtained when the cells were plated at the start of the experiment gave the value for toxicity.

Typical IC_{50} values for compounds of the invention when tested in the SRB assay are in the range 1mM to 1nM.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a pyrimidine derivative of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

According to a further aspect of the present invention there is provided a compound of

the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use in a method of treatment of the human or animal body by therapy.

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are effective cell cycle inhibitors (anti-cell proliferation agents), which property is believed to arise from their CDK inhibitory properties. Accordingly the compounds of the present invention are expected to be useful in the treatment of diseases or medical conditions mediated alone or in part by CDK enzymes, i.e. the compounds may be used to produce a CDK inhibitory effect in a warm-blooded animal in need of such treatment. Thus the compounds of the present invention provide a method for treating the proliferation of malignant cells characterised by inhibition of CDK enzymes, i.e. the compounds may be used to produce an anti-proliferative effect mediated alone or in part by the inhibition of CDKs. Such a compound of the invention is expected to possess a wide range of anti-cancer properties as CDKs have been implicated in many common human cancers such as leukaemia and breast, lung, colon, rectal, stomach, prostate, bladder, pancreas and ovarian cancer. Thus it is expected that a compound of the invention will possess anti-cancer activity against these cancers. It is in addition expected that a compound of the present invention will possess activity against a range of leukaemias, lymphoid malignancies and solid tumours such as carcinomas and sarcomas in tissues such as the liver, kidney, prostate and pancreas. In particular such compounds of the invention are expected to slow advantageously the growth of primary and recurrent solid tumours of, for example, the colon, breast, prostate, lungs and skin. More particularly such compounds of the invention, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, are expected to inhibit the growth of those primary and recurrent solid tumours which are associated with CDKs, especially those tumours which are significantly dependent on CDKs for their growth and spread, including for example, certain tumours of the colon, breast, prostate, lung, vulva and skin.

It is further expected that a compound of the present invention will possess activity against other cell-proliferation diseases in a wide range of other disease states including leukaemias, fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

Thus according to this aspect of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore for use as a medicament; and the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal such as man. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

According to a further feature of the invention there is provided the use of a compound of the formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

According to a further feature of this aspect of the invention there is provided a method for producing a cell cycle inhibitory (anti-cell-proliferation) effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound as defined immediately above. Particularly, an inhibitory effect is produced by preventing entry into or progression through the S phase by inhibition of CDK2, CDK4 and/or CDK6, especially CDK2.

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

The CDK inhibitory activity defined hereinbefore may be applied as a sole therapy or may involve, in addition to a compound of the invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. In the field of medical oncology it is normal practice to use a combination of different forms of treatment to treat each patient with cancer. In medical oncology the other component(s) of such conjoint treatment in addition to the cell cycle inhibitory treatment defined hereinbefore may be:

surgery, radiotherapy or chemotherapy. Such chemotherapy may cover three main categories of therapeutic agent:

(i) other cell cycle inhibitory agents that work by the same or different mechanisms from those defined hereinbefore;

(ii) cytostatic agents such as antioestrogens (for example tamoxifen,toremifene, raloxifene, droloxifene, iodoxyfene), progestogens (for example megestrol acetate), aromatase inhibitors (for example anastrozole, letrazole, vorazole, exemestane), antiprogestogens, antiandrogens (for example flutamide, nilutamide, bicalutamide, cyproterone acetate), LHRH agonists and antagonists (for example goserelin acetate, luprolide), inhibitors of testosterone 5α-dihydroreductase (for example finasteride), anti-invasion agents (for example metalloproteinase inhibitors like marimastat and inhibitors of urokinase plasminogen activator receptor function) and inhibitors of growth factor function, (such growth factors include for example platelet derived growth factor and hepatocyte growth factor such inhibitors include growth factor antibodies, growth factor receptor antibodies, tyrosine kinase inhibitors and serine/threonine kinase inhibitors); and

(iii) antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as antimetabolites (for example antifolates like methotrexate, fluoropyrimidines like 5-fluorouracil, purine and adenosine analogues, cytosine arabinoside); antitumour antibiotics (for example anthracyclines like doxorubicin, daunomycin, epirubicin and idarubicin, mitomycin-C, dactinomycin, mithramycin); platinum derivatives (for example cisplatin, carboplatin); alkylating agents (for example nitrogen mustard, melphalan, chlorambucil, busulphan, cyclophosphamide, ifosfamide, nitrosoureas, thiotepa); antimitotic agents (for example vinca alkaloids like vincrisitine and taxoids like taxol, taxotere); topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan). According to this aspect of the invention there is provided a pharmaceutical product comprising a compound of the formula (I) as defined hereinbefore and an additional anti-tumour substance as defined hereinbefore for the conjoint treatment of cancer.

In addition to their use in therapeutic medicine, the compounds of formula (I) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of in vitro and *in vivo* test systems for the evaluation of the effects of

inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following non-limiting examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates; where a silica Bond Elut column is referred to, this means a column containing 10g or 20g of silica of 40 micron particle size, the silica being contained in a 60ml disposable syringe and supported by a porous disc, obtained from Varian, Harbor City, California, USA under the name "Mega Bond Elut SI", "Mega Bond Elut" is a trademark;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) final products had satisfactory proton nuclear magnetic resonance (NMR) spectra and/or mass spectral data;

(vi) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vii) when given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-d_6) as solvent unless otherwise indicated;

(viii) chemical symbols have their usual meanings; SI units and symbols are used;

(ix) solvent ratios are given in volume:volume (v/v) terms; and

(x) mass spectra were run with an electron energy of 70 electron volts in the chemical

ionization (CI) mode using a direct exposure probe; where indicated ionization was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported;

(xi) unless stated otherwise compounds containing an asymmetrically substituted carbon and/or sulphur atom have not been resolved;

(xii) where a synthesis is described as being analogous to that described in a previous example the amounts used are the millimolar ratio equivalents to those used in the previous example;

(xvi) the following abbreviations have been used:

NMP	1-methyl-2-pyrrolidinone;
DMF	*N,N*-dimethylformamide;
DMFDMA	*N,N*-dimethylformamidedimethylacetyl;
DMSO	dimethylsulphoxide;
THF	tetrahydrofuran; and
EA	elemental analysis.

Example 1

2-(3-Chloroanilino)-4-(2-methylimidazo[1,2a]pyrid-3-yl)pyrimidine

Sodium hydride (236mg of a 60% suspension in mineral oil, 5.9mmol) was added to a solution of 3-chloroaniline (496ml, 4.7mmol) in NMP (10ml) under nitrogen. The mixture was stirred for 30 minutes at ambient temperature and a solution of 4-(2-methylimidazo[1,2a] pyrid-3-yl)-2-methylthiopyrimidine (Method 1) (600mg, 2.3mmol) in NMP (2ml) was added. The mixture was heated at 150°C for 3 hours. The reaction mixture was allowed to cool diluted with water and extracted with ethyl acetate. The combined extracts were dried and the volatiles removed by evaporation. The residue was purified by chromatography eluting with ethyl acetate/hexane (1:1) increasing in polarity to ethyl acetate/methanol (97:3). The purified product was triturated with ether and hexane, collected by filtration and dried to give the title compound (159mg, 21%). NMR: 2.62 (s, 3H), 6.98-7.04 (m, 2H), 7.12 (d, 1H), 7.25 (dd, 1H), 7.42 (dd, 1H), 7.59-7.64 (m, 2H), 8.02 (s, 1H), 8.55 (d, 1H), 9.72 (d, 1H), 9.84 (s, 1H).

Examples 2-12

Following the procedure of Example 1 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$
2	2-(4-Sulphamoylanilino)-4-(2-methylimidazo[1,2a]pyrid-3-yl) pyrimidine	2.64 (s, 3H), 7.05 (dd, 1H), 7.15-7.20 (m, 3H), 7.44 (dd, 1H), 7.64 (d, 1H), 7.74 (d, 2H), 7.92 (d, 2H), 8.68 (d, 1H), 9.75 (d, 1H)	381
3 [1]	2-Anilino-4-(2-methylimidazo [1,2a]pyrid-3-yl)pyrimidine	2.64 (s, 3H), 6.92-7.00 (m, 2H), 7.08 (d, 1H), 7.30 (dd, 1H), 7.40 (dd, 1H), 7.60 (d, 1H), 7.72 (d, 2H), 8.50 (d, 1H), 9.60 (s, 1H), 9.75 (d, 1H)	302
4	2-(4-Chloroanilino)-4-(2-methylimidazo[1,2a]pyrid-3-yl) pyrimidine	2.75 (s, 3H), 6.82 (dd, 1H), 7.01 (d, 1H), 7.22 (br s, 1H), 7.30 (m, 3H), 7.60 (m, 2H), 8.47 (d, 1H), 9.53 (d, 1H)	336
5 [1]	2-(3-Chloroanilino)-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	7.02 (d, 1H), 7.12 (dd, 1H), 7.30 (dd, 1H), 7.42 (d, 1H), 7.50 (dd, 1H), 7.60 (d, 1H), 7.75 (d, 1H), 8.00 (s, 1H), 8.48 (d, 1H), 8.61 (s, 1H), 9.82 (s, 1H)	322
6 [1]	2-(3,4-Dichloroanilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	7.15 (dd, 1H), 7.50 (dd, 2H), 7.58 (d, 1H), 7.65 (dd, 1H), 7.78 (d, 1H), 8.22 (d, 1H), 8.50 (d, 1H), 8.62 (s, 1H), 9.95 (s, 1H)	
7	2-(4-Sulphamoylanilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	7.20 (d, 3H), 7.55 (d, 2H), 8.80 (d, 3H), 8.95 (d, 2H), 8.50 (d, 1H), 8.68 (s, 1H), 10.05 (s, 1H), 10.10 (d, 1H)	367
8 [1]	2-(3-Chloro-4-fluoroanilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	7.14 (dd, 1H), 7.32-7.55 (m, 3H), 7.60 (dd, 1H), 7.78 (d, 1H), 8.10 (dd, 1H), 8.48 (d, 1H), 8.62 (s, 1H), 9.82 (s, 1H)	340
9	2-(2-Chloroanilino)-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	7.08 (dd, 1H), 7.17 (d, 1H), 7.37 (m, 2H), 7.48 (dd, 1H), 7.51 (br s, 1H), 7.62 (d, 1H), 7.76 (d, 1H), 8.30 (s, 1H), 8.40 (m, 1H), 9.81 (d, 1H), 9.94 (dd, 1H)	322

10	2-(2-Chloro-4-methylanilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	2.38 (s, 3H), 6.91 (dd, 1H), 7.14 (d, 1H), 7.28 (br s, 1H), 7.38 (m, 2H), 7.61 (s, 1H), 7.73 (d, 1H), 8.16 (d, 1H), 8.28 (s, 1H), 8.40 (d, 1H), 9.78 (d, 1H)	336
11 [1]	2-[4-(3,5-Dioxapiperidin-1-yl) sulphonylanilino]-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	4.87 (s, 2H), 5.20 (s, 4H), 7.16 (dd, 1H), 7.51 (d, 2H), 7.75 (d, 1H), 7.83 (d, 2H), 7.98 (d, 2H), 8.50 (d, 1H), 8.64 (s, 1H)	439
12 [1,2]	2-[4-(2-Diethylaminoethoxy) anilino]-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	0.98 (t, 6H), 2.50-2.62 (m, 4H), 2.78-2.82 (m, 2H), 4.00 (t, 2H), 6.84 (dd, 2H), 7.08 (dd, 1H), 7.38 (d, 1H), 7.48 (dd, 1H), 7.60 (s, 2H), 7.75 (d, 1H), 8.38 (d, 1H), 8.59 (s, 1H), 9.42 (s, 1H)	403

[1] Sodium bis(trimethylsilyl)amide (1M solution in THF) was used in place of sodium hydride.

[2] The product was purified by chromatography, eluting with dichloromethane / methanol (100:0 increasing to 80:20), triturated with ether and hexane and collected by filtration.

Example 13

2-[4-(3-Dimethylamino-2-hydroxypropoxy)anilino]-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

A mixture of 4-(3-dimethylamino-2-hydroxypropoxy)aniline (497mg, 1.76mmol) (Method 11) and cyanamide (185mg, 4.4mmol) in NMP (1ml) were heated at 160°C for 30 minutes. A mixture of 3-(3-dimethylaminoprop-2-en-1-oyl)imidazo[1,2a]pyridine (Method 5) (400mg, 1.76mmol) and sodium methoxide (183mg, 3.5mmol) in 1-butanol (10ml) was then added and the mixture heated at reflux for 3 hours. The mixture was allowed to cool and the residue was purified by chromatography, eluting with ethyl acetate/methanol (97:3 increasing in polarity to 90:10) to give the title compound (30mg, 4%). NMR: 2.35 (s, 6H), 2.40-2.63 (m, 2H), 3.82-4.02 (m, 3H), 6.90 (d, 2H), 7.06 (dd, 1H), 7.30 (d, 1H), 7.50 (dd, 1H), 7.59 (s, 2H), 7.74 (d, 1H), 8.38 (d, 1H), 8.58 (s, 1H), 9.42 (s, 1H); m/z: 405 $[MH]^+$.

Examples 14-15

Following the procedure of Example 13 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$
14 [1]	2-[4-(3-Dimethylamino-2-hydroxypropoxy)anilino]-4-(2-methylpyrazolo[2,3a]pyrid-3-yl) pyrimidine	2.20 (s, 6H), 2.26-2.45 (m, 2H), 2.65 (s, 3H), 3.80-3.95 (m, 3H), 4.80 (s, 1H), 6.88 (d, 2H), 7.00 (d, 2H), 7.38 (dd, 1H), 7.60 (d, 2H), 8.38 (d, 1H), 8.44 (d, 1H), 8.65 (d, 1H), 9.21 (s, 1H)	419
15 [2]	2-[4-(3-Dimethylamino-2-hydroxypropoxy)anilino]-4-(2-methylimidazo[1,2,a]pyrid-3-yl) pyrimidine	2.63 (s, 3H), 2.80 (s, 6H), 3.12-3.26 (m, 2H), 4.27 (br s, 1H), 5.93 (br s, 1H), 6.90-7.04 (m, 4H), 7.40 (t, 1H), 7.60 (dd, 2H), 8.45 (d, 1H), 9045 (s, 1H), 9.73 (d, 1H)	419

[1] Product was purified by chromatography eluting with dichloromethane/hexane (1:1) increasing in polarity to dichloromethane/methanol/triethylamine (96:4:0.5).

2 Product was purified by chromatography eluting with dichloromethane/methanol/ triethylamine (96:4:0.5) and recrystallized from acetonitrile/methanol.

Examples 16-36

The following examples were prepared, purified and characterised by the following generic method:

Sodium bis (trimethylsilyl)amide (2.05ml of a 1M solution in THF, 2.05mmol) was added to a solution of the aniline (1.65mmol) in NMP (1.5ml) under nitrogen. The mixture was stirred for 30 minutes at ambient temperature and a solution of 4-(imidazo[1,2a]pyrid-3-yl)-2-methylthiopyrimidine (Method 4) (200mg, 0.83mmol) in NMP (1ml) was added. The reaction mixture was heated at 150°C for 2.5 hours. The solvent and volatiles were removed by evaporation and the residue was purified by chromatography eluting with ethyl acetate, then ethyl acetate/methanol (97:3) and finally ethyl acetate/methanol (97:3). The reaction products were characterised by HPLC on a 4.6mm x 10cm Hichrom RPB 100A column eluting water/acetonitrile/formic acid (95:5:0.1 for 1.5

minutes then on a 10 minute gradient to 5:95:0.1) with a flow rate of 1.0ml/minute, detecting at 254nm (bandwidth 10nm).

Ex	Compound	HPLC Ret Time (mins)	M/z $[MH]^+$
16	2-Anilino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.26	288
17	2-(2-Fluoroanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.26	306
18	2-(3-Bromoanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	8.30	368
19	2-(3-Fluoroanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.70	306
20	2-(3-Methoxyanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.39	318
21	2-(3-Methylthioanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.98	334
22	2-(3-Acetylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.13	330
23	2-(3-Ethylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	8.11	316
24	2-(4-Fluoroanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.47	306
25	2-(4-Chloroanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	8.15	322
26	2-(4-Methoxyanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.02	318
27	2-(4-Benzyloxyanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	8.65	394
28	2-[4-(Anilinosulphonyl)anilino]-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	7.79	443
29	2-(4-Mesylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	6.84	366
30	2-(4-Methylthioanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.89	334
31	2-(4-Methylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.65	302
32	2-(3-Sulphamoylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	6.30	367
33	2-[4-(Pyrimid-2-ylaminosulphonyl)anilino]-4-(imidazo[1,2a] pyrid-3-yl)pyrimidine	6.72	445
34	2-(4-Phenoxyanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	8.86	380
35	2-(3-Methylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	7.63	302
36	2-(Indan-5-ylamino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	8.20	328

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Example 37

2-(3-Chloroanilino)-4-(2,5-dimethylimidazo[1,2a]pyrid-3-yl)pyrimidine

2-Methylthio-4-(2,5-dimethylimidazo[1,2a]pyrid-3-yl)pyrimidine (Method 14) (200mg, 0.74 mmol) was added to a solution of 3-chloroaniline (0.16ml, 1.48mmol) and sodium hydride (60mg, 1.48mmol) in NMP (1ml) under nitrogen. The mixture was heated at 150°C for 4 hours and then allowed to cool. The crude reaction mixture was loaded onto a Bond Elut column eluting with dichloromethane to remove the NMP and then with dichloromethane/methanol/methylamine (75:20:5) to elute the product. The product was further purified by chromatography eluting with ethyl acetate/hexane (8:2) and then ethyl acetate to give the title compound (22mg, 9%). NMR: 2.27 (s, 3H), 2.61 (s, 3H), 7.01 (d, 1H), 7.12 (d, 1H), 7.30 (m, 2H), 7.56 (d, 1H), 7.62 (d, 1H), 8.57 (d, 1H), 9.41 (s 1H), 9.83 (s, 1H); m/z: 350 $[MH]^+$.

Example 38

Following the procedure of Example 37 and using the appropriate starting materials the following compound was prepared.

Ex	Compound	NMR	m/z $[MH]^+$
38	2-(3-Chloroanilino)-4-(2-methylpyrazolo[2,3a]pyrid-3-yl) pyrimidine	2.64 (s, 3H), 6.95-7.03 (m, 2H), 7.17 (d, 1H), 7.32 (d, 1H), 7.44 (dd, 1H), 7.58-7.64 (m, 2H), 8.04 (s, 1H), 8.57 (d, 1H), 9.72 (d, 1H), 9.84 (s, 1H)	336

Example 39

2-[4-(*N*-Methylsulphamoyl)anilino]-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

Toluene (4ml) was added to a mixture of tris(dibenzideneacetone)dipalladium(0) (24mg, 0.026mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (21mg, 0.034mmol), 2-chloro-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Method 20; 150mg, 0.652mmol) and 4-(*N*-methylsulphamoyl)aniline (Method 23; 135mg, 0.725mmol) under nitrogen. The flask was evacuated and refilled with nitrogen and sodium *tert*-butoxide (140mg, 1.46mmol) was added and the flask was re-evacuated and refilled with nitrogen. The mixture was heated at 100°C for 3 hours and then allowed to cool. The mixture was diluted with ethyl

acetate and washed with water. The organic phase was separated, dried and the volatiles removed by evaporation. The residue was purified by chromatography eluting with ethyl acetate / methanol (100:0 increasing in polarity to 97:3) to give the title compound 15mg, (60%). NMR: 2.42 (d, 3H), 7.25-7.10 (m, 2H), 7.52-7.45 (m, 2H), 7.79-7.70 (m, 3H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H); m/z: 381 $[MH]^+$.

Examples 40-44

Following the procedure of Example 39 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$	SM
40[1]	2-{4-[*N*-(2-Methoxyethyl) sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	2.90 (q, 2H), 3.18 (s, 3H), 3.28-3.30 (m, 2H), 7.16 (dd, 1H), 7.48-7.54 (m, 3H), 7.71-7.80 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	425	Meth 24
41[2]	2-[4-(*N*-Propylsulphamoyl) anilino]-4-(imidazo[1,2a] pyrid-3-yl)pyrimidine	0.80 (t, 3H), 1.34-1.42 (m, 2H), 2.65-2.75 (m, 2H), 7.15 (dd, 1H) 7.17 (dd, 1H), 7.55-7.48 (m, 2H), 7.70-7.79 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.63 (s, 1H)	409	Meth 25
42	2-[4-(*N*-Cyclopropyl-sulphamoyl)anilino]-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	0.00-0.05 (m, 2H), 0.09-0.12 (m, 2H), 1.70-1.75 (m, 1H), 6.79 (dd, 1H), 7.10-7.15 (m, 2H), 7.32-7.42 (m, 4H), 7.60 (d, 2H), 8.12 (d, 1H), 8.28 (s, 1H), 9.74 (s, 1H), 9.75 (s, 1H)	405 $[M-H]^-$	Meth 26
43	2-[4-(*N,N*-Dimethyl-carbamoyl)anilino]-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	2.98 (s, 6H), 7.10 (dd, 1H), 7.3.8-7.50 (m, 3H), 7.72-7.82 (m, 3H), 8.45 (d, 1H), 8.61 (s, 1H), 9.82 (s, 1H)	359	
44[3]	2-[4-(*N*-Methylcarbamoyl)	2.78 (d, 3H), 7.15 (dd, 1H), 7.43	345	

	anilino]-4-(imidazo[1,2a] pyrid-3-yl)pyrimidine	(d, 1H), 7.50 (dd, 1H), 7.75-7.82 (m, 5H), 8.24 (d, 1H), 8.48 (d, 1H), 8.62 (s, 1H), 9.90 (s, 1H)		

[1] Product was purified by chromatography eluting with hexane/ethyl acetate (70:30) increasing in polarity to (0:100).

[2] Product was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (95:5).

[3] Product was purified by chromatography eluting with hexane/ethyl acetate (80:20) increasing in polarity to ethyl acetate/methanol (90:10).

Example 45

2-{4-[*N*-(3-Hydroxypropyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

2-Anilino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Example 16; 100mg, 0.347mmol) was dissolved in thionyl chloride (4ml) and the mixture was cooled to 5°C. Chlorosulphonic acid (0.06ml, 0.90mmol) was added and the was mixture stirred at 5°C for 30 minutes, then allowed to warm to ambient temperature and stirred for 60 minutes. The mixture was then heated at reflux for 90 minutes. The volatiles were removed by evaporation and the residue azeotroped with toluene. 3-Aminopropanol (3ml) was added to residue and the mixture stirred at ambient temperature for 30 minutes. The mixture was purified chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (85:15). 60mg (41%). NMR: 1.45-1.56 (m, 2H), 2.79 (q, 2H), 3.35 (q, 2H), 4.39 (t, 1H), 7.15 (dd, 1H), 7.31 (t, 1H), 7.45-7.54 (m, 2H), 7.70-7.79 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H); m/z: 423 $[M-H]^-$.

Examples 46-50

Following the procedure of Example 45 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$
46	2-{4-[*N*-(Cyclopropylmethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	0.00-0.04 (m, 2H), 0.25-0.32 (m, 2H), 0.70-0.78 (m, 1H), 2.60 (t, 2H), 7.10 (dd, 1H), 7.28-7.42 (m, 3H), 7.68-7.75	421

		(m, 3H), 7.87 (d, 2H), 8.42 (d, 1H), 8.60 (s, 1H)	
47	2-{4-[*N*-(5-Hydroxypentyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.18-1.40 (m, 8H), 2.70 (t, 2H) 4.25 (br s, 1H), 7.15 (dd, 1H), 7.48-7.52 (m, 2H), 7.70-7.78 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	453
48	2-(4-{*N*-[2-(1-Methylpyrrolidin-2-yl)ethyl]sulphamoyl}anilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	1.18-1.25 (m, 2H), 1.48-1.58 (m, 2H), 1.60-1.70 (m, 1H), 1.90-2.00 (m, 2H), 2.10 (s, 3H), 2.70-2.85 (m, 4H), 7.15 (dd, 1H), 7.40 (s, 1H), 7.48-7.53 (m, 2H), 7.70-7.80 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.63 (s, 1H)	476 $[M-H]^-$
49	2-{4-[*N*-(3-Diethylaminopropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	0.86 (t, 6H), 1.42 (q, 2H), 2.30 (q, 4H), 2.38-2.42 (m, 2H), 2.75 (q, 2H), 7.15 (dd, 1H), 7.42-7.55 (m, 2H), 7.70-7.80 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.65 (s, 1H)	480
50	2-{4-[*N*-(2-Isopropylaminoethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	0.87 (s, 3H), 0.90 (s, 3H), 2.46-2.50 (m, 2H), 2.58 (q, 2H), 2.80 (t, 2H), 7.18 (dd, 1H), 7.48-7.52 (m, 2H), 7.70-7.80 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	452

[1] Product was purified by chromatography eluting with hexane/ethyl acetate (70:30) increasing in polarity to (0:100)

[2] Product was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (95:5).

[3] Product was purified by chromatography eluting with hexane/ethyl acetate (80:20) increasing in polarity to ethyl acetate/methanol (90:10).

Example 51

2-(4-{*N*-[3-(2-Oxopyrolidin-1-yl)propyl]sulphamoyl}anilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine

2-Anilino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Example 16; 100mg, 0.347mmol) was dissolved in thionyl chloride (3ml) and the mixture was cooled to 5°C. Chlorosulphonic acid (0.06ml, 0.90mmol) was added and the was mixture stirred at 5°C for 30 minutes, allowed to warm to ambient temperature and stirred for 60 minutes. The mixture was then heated at reflux for 90 minutes. The volatiles were removed by evaporation and the residue azeotroped with toluene. Pyridine (3ml) and 3-(2-oxopyrolidin-1-yl)propylamine (3ml) were added to the residue and the mixture was stirred at ambient temperature for one hour. The mixture was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (80:20). 60mg (36%). NMR: 1.51-1.60 (m, 2H), 1.80-1.90 (m, 2H), 2.13 (t, 2H), 2.70 (t, 2H), 3.10 (t, 2H), 3.20 (t, 2H), 7.16 (dd, 1H), 7.48-7.55 (m, 2H), 7.70-7.80 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H); m/z: 492 $[MH]^+$.

Examples 52-70

Following the procedure of Example 45 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$
52	2-{4-[*N*-(3-Methoxypropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.55-1.62 (m, 2H), 2.75-2.81 (m, 2H), 3.12 (s, 3H), 3.23-3.28 (m, 2H), 7.15 (dd, 1H), 7.38 (t, 1H), 7.55 (m, 2H), 7.70-7.80 (m, 3H), 7.96 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	439
53	2-{4-[*N*-(3-Isopropylaminopropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.48 (t, 2H), 1.88 (d, 6H), 2.42 (t, 2H), 2.59 (m, 1H), 2.79 (t, 2H), 7.15 (dd, 1H), 7.48-7.55 (m, 2H), 7.70-7.80 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	466
54	2-{4-[*N*-(3-Imidazol-1-ylpropyl)	1.80 (m, 2H), 2.70 (q, 2H), 3.94 (t, 2H),	473

	sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	6.82 (s, 1H), 7.08 (s, 1H), 7.14 (dd, 1H), 7.48-7.52 (m, 4H), 7.70 (d, 2H), 7.78 (d, 1H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	$[M-H]^-$
55[1]	2-{4-[*N*-(3-Dimethylaminopropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.48 (m, 2H), 2.02 (s, 6H), 2.12 (t, 2H), 2.78 (t, 2H), 7.15 (dd, 1H), 7.38 (s, 1H), 7.48-7.57 (m, 2H), 7.72 (d, 2H), 7.78 (d, 1H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	452
56	2-{4-[*N*-(3-Morpholinopropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.52 (t, 2H), 2.18-2.22 (m, 6H), 2.78 (t, 2H), 3.43-3.48 (m, 4H), 7.15 (dd, 1H), 7.38 (s, 1H), 7.48-7.55 (m, 2H), 7.74 (d, 2H), 7.78 (d, 1H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	494
57[1]	2-{4-[*N*-(3-Aminopropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.38-1.45 (m, 4H), 2.79 (t, 2H), 7.15 (dd, 1H), 7.48-7.56 (m, 2H), 7.60-7.64 (m, 1H), 7.72 (d, 2H), 7.79 (d, 1H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	424
58[1]	2-(4-{*N*-[2-(2-Hydroxyethyl amino)ethyl]sulphamoyl}anilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	2.75 (t, 2H), 2.86-2.90 (m, 2H), 3.54 (t, 2H), 3.60 (t, 2H), 7.08 (d, 2H), 7.18 (dd, 1H), 7.42-7.55 (m, 2H), 7.75-7.80 (m, 3H), 8.00 (d, 2H), 8.52 (d, 1H), 8.62 (s, 1H)	454
59[2]	2-{4-[*N*-(2-Imidazol-4-ylethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	3.10 (t, 2H), 3.95 (t, 2H), 7.10 (d, 2H), 7.40 (s, 2H), 7.50 (d, 2H), 7.58 (d, 2H), 7.69 (d, 2H), 7.75 (d, 1H), 8.45 (d, 1H), 8.60 (s, 1H), 8.79 (s, 1H), 9.75 (s, 1H), 10.1 (s, 1H)	
60[1]	2-{4-[*N*-(3-Methylaminopropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.70-1.78 (m, 2H), 2.66 (s, 3H), 2.90 (t, 2H), 3.00 (t, 2H), 7.08 (d, 2H), 7.18 (t, 1H), 7.44 (d, 2H), 7.51 (m, 1H), 7.70-7.80 (m, 3H), 8.02 (d, 1H), 8.52 (d,	436 $[M-H]^-$

		1H), 8.63 (s, 1H)	
61[1]	2-{4-[*N*-(2-Piperazin-1-ylethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	2.30 (t, 2H), 2.40-2.43 (m, 4H), 2.59 (t, 2H), 2.83-2.90 (m, 4H), 7.18 (dd, 1H), 7.49-7.55 (m, 2H), 7.68 (d, 2H), 7.78 (d, 1H), 8.02 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	
62[1]	2-(4-{*N*-[3-(4-Methylpiperazin-1-yl)propyl]sulphamoyl}anilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	1.49 (m, 2H), 2.10 (s, 3H), 2.15-2.25 (m, 8H), 2.78 (q, 2H), 3.25-3.29 (m, 2H), 7.18 (dd, 1H), 7.40 (dd, 1H), 7.50 (d, 2H), 7.75 (d, 2H), 8.80 (d, 1H), 7.95 (d, 1H), 8.52 (d, 1H), 8.65 (s, 1H)	507
63[1]	2-(4-{*N*-[2-(2-Diethylaminoethyl-amino)ethyl]sulphamoyl}anilino)-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	0.93 (t, 6H), 2.40-2.58 (m, 4H), 2.62 (t, 2H), 2.84 (t, 2H), 3.20-3.40 (m, 4H), 7.10 (d, 1H), 7.18 (dd, 1H), 7.42-7.50 (m, 3H), 7.72-7.80 (m, 3H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	509
64[1]	2-{4-[*N*-(2,3-Dihydroxypropyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	2.66 (m, 1H), 2.86 (m, 1H), 3.21-3.30 (m, 2H), 3.46 (m, 1H), 4.49 (t, 1H), 4.70 (d, 1H), 7.18 (dd, 1H), 7.24 (dd, 1H), 7.48-7.52 (m, 2H), 7.70-7.80 (m, 3H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	441
65	2-{4-[*N*-(2-Dimethylaminoethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	2.08 (s, 6H), 2.24 (t, 2H), 2.82 (t, 2H), 1.7 (dd, 1H), 7.30 (s, 1H), 7.44-7.54 (m, 2H), 7.70-7.80 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.63 (s, 1H)	438
66	2-{4-[*N*-(2-Morpholinoethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	2.34-2.45 (m, 6H), 2.87-2.95 (m, 2H), 3.46-3.60 (m, 4H), 7.09 (d, 2H), 7.18 (dd, 1H), 7.42-7.50 (m, 3H), 7.74-7.80 (m, 2H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	478 $[M-H]^-$

67	2-{4-[*N*-(2-Pyrrolidin-1-ylethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.64-1.74 (m, 4H), 2.52-2.64 (m, 6H), 2.87-2.92 (m, 2H), 7.18 (dd, 1H), 7.44-7.54 (m, 3H), 7.72-7.80 (m, 3H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	464
68	2-{4-[*N*-(2-Methylaminoethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	2.61-2.64 (m, 2H), 2.68 (s, 3H), 2.90 (t, 2H), 7.18 (dd, 1H), 7.48-7.58 (m, 2H), 7.68-7.78 (m, 4H), 7.95 (d, 1H), 8.00 (d, 1H), 8.51 (d, 2H), 8.64 (s, 1H)	424
69	2-{4-[*N*-(2-Piperidin-1-ylethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	1.28-1.40 (m, 2H), 1.40-1.58 (m, 4H), 2.20-2.50 (m, 6H), 2.84-2.92 (m, 2H), 7.18 (dd, 1H), 7.48-7.53 (d, 2H), 7.72-7.80 (m, 3H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	478
70	2-{4-[*N*-(2-Diethylaminoethyl) sulphamoyl]anilino}-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine	0.86 (t, 6H), 2.32-2.42 (m, 6H), 2.79 (t, 2H), 7.18 (dd, 1H), 7.23 (s, 1H), 7.48-7.52 (m, 2H), 7.70-7.80 (m, 3H), 7.98 (d, 2H), 8.50 (d, 1H), 8.62 (s, 1H)	466

[1] Product was purified by chromatography eluting with ethyl acetate/methanol (100:0) increasing in polarity to (70:30)

[2] Product was isolated without chromatography by trituration from reaction mixture with dichloromethane and methanol.

Example 71

2-{4-[*N*-(3-Imidazol-1-ylpropyl)carbamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

Toluene (10ml) was added to 2-amino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Method 22; 200mg, 0.95mmol), 1-[3-(4-bromobenzoylamino)propyl]imidazole (Method 27; 350mg, 1.14mmol), tris(dibenzideneacetone)dipalladium(0) (43mg, 0.047mmol) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (28mg, 0.046mmol) under nitrogen. Sodium *tert*-butoxide (218mg, 0.0023mmol) was added, the reaction mixture was flushed thoroughly with nitrogen and then heated at 100°C for 24 hours. The volatiles were removed by evaporation and the residue was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (95:5) to give the title compound

99mg (24%). NMR: 1.90-2.00 (m, 2H), 3.22 (q, 2H), 4.02 (t, 2H), 6.86 (s, 1H), 7.16 (dd, 1H), 7.21 (s, 1H), 7.42-7.55 (m, 2H), 6.80 (s, 3H), 7.78 (d, 1H), 7.83 (s, 4H), 8.38 (t, 1H), 8.48 (d, 1H), 8.62 (s, 1H), 9.92 (s, 1H); m/z: 439 $[MH]^+$.

Examples 72-74

Following the procedure of Example 71 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$	SM
72[1]	2-(4-{*N*-[3-(2-Oxopyrolidin-1-yl)propyl]carbamoyl} anilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine	1.70 (quin, 2H), 1.90 (quin, 2H), 2.21 (t, 2H), 3.18-3.24 (m, 4H), 3.30-3.38 (m, 2H), 7.15 (dd, 1H), 7.42-7.52 (m, 2H), 7.78 (d, 1H), 7.82 (s, 4H), 8.27 (t, 1H), 8.49 (d, 1H), 8.62 (s, 1H), 9.90 (s, 1H).	456	Meth 28
73[2]	2-{3-Chloro-4-[*N*-(2-methoxyethyl)sulphamoyl] anilino}-4-(imidazo[1,2a] pyrid-3-yl)pyrimidine	3.00 (q, 2H), 3.12 (s, 3H), 3.25-3.30 (m, 2H), 7.18 (dd, 1H), 7.50-7.58 (m, 2H), 7.68 (t, 1H), 7.75-7.80 (m, 2H), 7.87 (s, 1H), 8.22 (s, 1H), 8.55 (d, 1H), 8.64 (s, 1H)	459	
74[3]	2-[3-Chloro-4-(*N*-propyl sulphamoyl)anilino]-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	0.80 (t, 3H), 1.38 (m, 2H), 2.79 (q, 2H), 7.18 (dd, 1H), 7.48-7.55 (m, 2H), 7.66 (dd, 1H), 7.78 (dd 2H), 7.92 (d, 1H), 8.25 (s, 1H), 8.55 (d, 1H), 8.68 (s, 1H), 10.10 (d, 1H), 10.26 (s, 1H)	443	

[1] Reaction heated at 100°C for 48 hours and purified by chromatography eluting with dichloromethane/methanol (90:10)

[2] Starting from 2,4-dichloro-1-(2-methoxyethylsulphamoyl)benzene (Method 29)

[3] Starting from 2,4-dichloro-1-(1-propylsulphamoyl)benzene (Method 30)

Example 75

2-(3-Methyl-4-sulphamoylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

2-(3-Methylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Example 35; 80mg, 0.266mmol) was treated as described in Example 45 but with 2M ethanolic ammonia to give the title compound (6mg, 17%). NMR: 2.60 (s, 3H), 6.95-7.20 (m, 4H), 7.46-7.50 (m, 2H), 7.70-7.80 (m, 4H), 8.50 (d, 1H), 8.62 (s, 1H), 9.87 (s, 1H); m/z: 381 $[MH]^+$.

Examples 76-78

Following the procedure of Example 75 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$
76	2-{3-Methyl-4-[*N*-(2-methoxy-ethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	2.55 (s, 3H), 2.91 (q, 2H), 3.11 (s, 3H), 3.22 (t, 2H), 7.12 (dd, 1H), 7.44-7.55 (m, 3H), 7.74-7.80 (m, 4H), 8.50 (d, 1H), 8.62 (s, 1H), 9.98 (s, 1H)	439
77	2-{3-Methyl-4-[*N*-(3-morpholino-propyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	1.49 (m, 2H), 2.13-2.20 (m, 4H), 3.24-3.32 (m, 2H), 2.58 (s, 3H), 2.80 (t, 2H), 3.42-3.48 (m, 4H), 7.12 (dd, 1H), 7.48-7.53 (m, 2H), 7.75-7.80 (m, 4H), 8.50 (d, 1H), 8.62 (s, 1H)	508
78	2-{3-Methyl-4-[*N*-(2-morpholino-ethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	2.18-2.21 (m, 4H), 2.30-3.38 (m, 2H), 2.59 (s, 3H), 2.87 (t, 2H), 3.42-3.48 (m, 4H), 7.12 (dd, 1H), 7.42-7.55 (m, 3H), 7.75-7.80 (m, 4H), 8.50 (d, 1H), 8.62 (s, 1H), 9.98 (s, 1H)	494

Example 79

5-Bromo-2-(4-sulphamoylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

2-Anilino-5-bromo-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Example 97; 73mg, 0.2mmol) was treated as described in Example 45 but with 2M ethanolic ammonia to give the

title compound (18mg, 21%). NMR: 7.12 (dd, 1H), 7.19 (s, 2H), 7.53 (dd, 2H), 7.72 (d, 2H), 7.79 (d, 1H), 7.84 (d, 2H), 8.76 (s, 1H), 8.78 (s, 1H), 9.62 (s, 1H); m/z: 445 $[MH]^+$.

Examples 80-81

Following the procedure of Example 79 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$
80	5-Bromo-2-{4-[*N*-(2-methoxy-ethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	2.90 (m, 2H), 3.18 (s, 3H), 3.28 (q, 2H), 7.10 (dd, 1H), 7.48-7.58 (m, 2H), 7.70 (d, 2H), 7.79 (d, 1H), 7.86 (d, 2H), 8.76 (s, 1H), 8.78 (s, 1H), 9.66 (d, 1H)	503
81	5-Bromo-2-{4-[*N*-(2-dimethyl-aminoethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	2.06 (s, 6H), 2.25 (t, 2H), 2.82 (t, 2H), 7.15 (dd, 1H), 7.30 (s, 1H), 7.55 (dd, 1H), 7.72 (d, 2H), 7.80 (d, 1H), 7.90 (d, 2H), 8.75 (s, 1H), 9.80 (s, 1H), 9.65 (d, 1H), 10.28 (s, 1H)	516
82[1]	5-Bromo-2-{4-[*N*-(3-dimethyl-aminopropyl)sulphamoyl]anilino} - 4-(imidazo[1,2a]pyrid-3-yl) pyrimidine	1.70-1.80 (m, 2H), 1.87-1.98 (m, 2H), 2.62 (d, 6H), 2.79 (q, 2H), 7.12 (dd, 1H), 7.55 (dd, 1H), 7.59 (dd, 1H), 7.70 (d, 2H), 7.79 (d, 1H), 7.90 (d, 2H), 8.78 (s, 1H), 8.79 (s, 1H), 9.64 (d, 1H), 10.32 (s, 1H)	530

[1] Product was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (70:30)

Example 83

2-{4-[*N*-(2-Methoxyethyl)sulphamoyl]anilino}-4-(5-bromoimidazo[1,2a]pyrid-3-yl) pyrimidine

2-Anilino-4-(5-bromoimidazo[1,2a]pyrid-3-yl)pyrimidine (Example 98; 70mg, 0.2mmol) was treated with 2-methoxyethylamine under the conditions described in Example 51 to give the title compound 23mg (25%). NMR: 2.90 (q, 2H), 3.18 (s, 3H), 3.26-3.29 (m,

2H), 7.49-7.54 (m, 2H), 7.60 (dd, 1H), 7.74-7.78 (m, 3H), 7.90 (d, 1H), 8.54 (d, 1H), 8.62 (s, 1H); m/z: 503 $[MH]^+$.

Example 84

2-{4-[*N*-(2-Methoxyethyl)sulphamoyl]anilino}-4-(5-phenylthioimidazo[1,2a]pyrid-3-yl) pyrimidine

Sodium hydride (80mg of a 60% suspension in mineral oil, 2.0mmol) was added to thiophenol (0.102ml, 1.0mmol) in NMP (4ml) and the mixture was stirred for 30 minutes. 2-[4-(*N*-(2-Methoxyethyl)sulphamoyl)anilino]-4-(5-bromoimidazo[1,2a]pyrid-3-yl)pyrimidine (Example 83; 100mg, 0.19mmol) in NMP (1ml) was added and the mixture was heated at 150°C for 18 hours. The mixture was allowed to cool, diluted with water and extracted with ethyl acetate. The extracts were washed with water, dried and the volatiles removed by evaporation. The residue was triturated with ether and collected by filtration to give the title compound 20mg (20%). NMR: 2.85 (q, 2H), 3.15 (s, 3H), 3.24 (q, 2H), 7.10-7.30 (m, 5H), 7.38 (d, 1H), 7.46 (dd, 1H), 7.52 (d, 1H), 7.75 (d, 2H), 7.79 (d, 1H), 7.92 (d, 2H), 8.54 (d, 1H), 8.66 (s, 1H); m/z: 533 $[MH]^+$.

Examples 85-88

Following the procedure of Example 84 and using the appropriate starting materials the following compounds were prepared.

Ex	Compound	NMR	m/z $[MH]^+$
85[1]	2-{4-[*N*-(2-Methoxyethyl) sulphamoyl]anilino}-4-(5-ethyl-thioimidazo[1,2a]pyrid-3-yl) pyrimidine	1.18 (t, 3H), 2.84-2.95 (m, 4H), 3.18 (s, 3H), 3.26-3.30 (m, 2H), 7.49-7.58 (m, 3H), 7.71-7.79 (m, 4H), 7.90 (d, 2H), 8.50-8.55 (m, 1H), 8.60 (s, 1H), 8.89 (s, 1H)	485
86[1]	2-{4-[*N*-(2-Methoxyethyl) sulphamoyl]anilino}-4-[5-(2-hydroxyethylthio)imidazo[1,2a] pyrid-3-yl]pyrimidine	2.90 (t, 2H), 3.05 (t, 2H), 3.20 (s, 3H), 3.32 (t, 2H), 3.60 (q, 2H), 5.00 (t, 1H), 7.45 (dd, 1H), 7.50 (d, 1H), 7.58 (d, 1H), 7.70-7.79 (m, 3H), 7.95 (d, 2H), 8.50 (d, 1H), 8.59 (s, 1H), 9.95 (s, 1H),	501

		10.05 (s, 1H)	
87[2]	2-{4-[*N*-(2-Methoxyethyl) sulphamoyl]anilino}-4-[5-(thien-2 -ylthio)imidazo[1,2a]pyrid-3-yl]pyrimidine	2.90 (m, 2H), 3.15 (s, 3H), 3.24 (q, 2H), 7.08-7.10 (m, 1H), 7.32 (d, 1H), 7.42 (d, 1H), 7.50 (d, 1H), 7.70-7.80 (m, 4H), 7.94 (d, 2H), 8.52 (d, 1H), 8.63 (s, 1H)	539
88[3]	2-{4-[*N*-(2-Methoxyethyl) sulphamoyl]anilino}-4-[5-(2-dimethylaminoethylthio)imidazo [1,2a]pyrid-3-yl]pyrimidine	2.15 (s, 6H), 2.40-2.50 (m, 2H), 2.90 (q, 2H), 3.09 (t, 2H), 3.20 (s, 3H), 3.28-3.32 (m, 2H), 7.48-7.58 (m, 3H), 7.72-7.80 (m, 3H), 7.95 (d, 2H), 8.51 (d, 1H), 8.60 (s, 1H), 9.90 (s, 1H), 10.11 (s, 1H)	528

[1] Product was purified by chromatography eluting with ethyl acetate/methanol (100:0) increasing in polarity to (95:5)

[2] Product was purified by chromatography eluting with ethyl acetate

[3] Product was purified by chromatography eluting with ethyl acetate/methanol (100:0) increasing in polarity to (70:30)

Example 89

2-{4-[*N*-(2-Methoxyethyl)sulphamoyl]anilino}-4-(5-cyanoimidazo[1,2a]pyrid-3-yl)pyrimidine

2-{4-[*N*-(2-Methoxyethyl)sulphamoyl]anilino}-4-(5-bromoimidazo[1,2a]pyrid-3-yl) pyrimidine (Example 83; 87mg, 0.17mmol), tetraethylammonium cyanide (27mg, 0.17mmol), diphenylphosphinoferrocene (23mg, 0.03mmol) copper (I) cyanide (62mg, 0.7mmol) and tris(dibenzideneacetone)dipalladium(0) (7mg, 0.008mmol) in dry dioxane (6ml) was flushed thoroughly with nitrogen and heated at reflux for 48 hours. The volatiles were removed by evaporation and the residue was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to (0:100) to give the title compound 16mg (21%). NMR: 2.90 (q, 2H), 3.15 (s, 3H), 3.25-3.30 (m, 2H), 7.42 (dd, 1H), 7.58 (d, 1H), 7.72-7.78 (m, 3H), 7.90-7.98 (m, 3H), 8.59 (d, 1H), 8.40 (s, 1H), 10.23 (s, 1H), 10.53 (s, 1H); m/z: 447 $[M-H]^-$.

Example 90

2-{4-[*N*-(3-Dimethylaminopropyl)sulphamoyl]anilino}-4-(5-bromoimidazo[1,2a]pyrid-3-yl) pyrimidine

2-Anilino-4-(5-bromoimidazo[1,2a]pyrid-3-yl)pyrimidine (Example 98; 200mg, 0.52mmol) was treated as described in Example 45 but treated with 3-dimethylaminopropyl-amine to give the title compound (92mg, 34%). NMR: 1.48-1.58 (m, 2H), 2.10 (s, 6H), 2.20-2.28 (m, 2H), 2.72-2.80 (m, 2H), 7.08 (d, 1H), 7.40-7.48 (m, 2H), 7.51 (d, 1H), 7.61 (dd, 1H), 7.71-7.78 (m, 3H), 7.90 (d, 2H), 8.55 (d, 1H), 8.64 (s, 1H); m/z: 530 $[MH]^+$.

Example 91

5-(2-Hydroxyethylthio)-2-{4-[*N*-(2-Methoxyethyl)sulphamoyl]anilino}-4-(imidazo[1,2a] pyrid-3-yl)pyrimidine

Sodium hydride (158mg of a 60% suspension in mineral oil, 4.0mmol) was added to 2-mercaptoethanol (0.139ml, 2.0mmol) in NMP (4ml) and the mixture was stirred for 30 minutes. 5-Bromo-2-{4-[*N*-(2-methoxyethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine (Example 80; 100mg, 0.19mmol) in NMP (1ml) was added and the mixture was heated at 120°C for 3 hours. The mixture was allowed to cool, diluted with water, neutralised with 2M hydrochloric acid and extracted with ethyl acetate. The extracts were washed with water and brine, dried and the volatiles removed by evaporation. The residue was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (95:5) to give the title compound 39mg (20%). NMR: 2.85-2.98 (m, 4H), 3.15 (s, 3H), 3.24-3.30 (m, 2H), 3.51 (q, 2H), 4.82 (t, 1H), 7.10 (dd, 1H), 7.45-7.54 (m, 2H), 7.70 (d, 2H), 7.78 (d, 1H), 7.90 (d, 2H), 8.70 (s, 1H), 8.85 (s, 1H), 9.72 (d, 1H), 10.18 (s, 1H); m/z: 501 $[MH]^+$.

Example 92

2-(4-{*N*-[3-(*tert*-Butoxycarbonylamino)propyl]sulphamoyl}anilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

2-Anilino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Example 16; 290mg, 1.0mmol) was dissolved in thionyl chloride (6ml) and the mixture was cooled to 0°C. Chlorosulphonic acid (0.266ml, 4.0mmol) was added slowly and the mixture was stirred at 0°C for 30 minutes, allowed to warm to ambient temperature stirred for two hours and then heated at reflux for one hour. The volatiles were removed by evaporation. The residue was dissolved in dry

pyridine (5ml) and the resulting solution added slowly to a solution of 3-(tert-butoxycarbonylamino)propylamine (0.209ml, 1.2mmol) and diethylmethylamine (1.21ml, 10mmol) in pyridine (10ml) and cooled to 0°C under nitrogen. The mixture was stirred at 0°C for one hour, then at ambient temperature for two hours. The volatiles were removed by evaporation and the residue azeotroped with water. The residue was triturated with water, collected by filtration, and then purified by chromatography eluting with dichloromethane/methanol (95:5) increasing in polarity to (90:10) to give the title compound 207 mg, (40%). NMR: 1.30 (s, 9H), 1.50 (quin, 2H), 2.67 (m, 2H), 2.85 (m, 2 H), 7.38 (m, 2H), 7.58 (d, 1H), 7.68 (d, 1H), 7.70 (d, 2H), 7.89 (d, 1H), 7.95 (d, 2H), 8.58 (d, 1H), 8.80 (s, 1H); m/z: 524 $[MH]^+$.

Example 93

2-(4-{*N*-[3-(Benzyloxycarbonylamino)propyl]sulphamoyl}anilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

2-Anilino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Example 16; 290mg, 1.0mmol) and 3-(benzyloxycarbonylamino)propylamine (0.294ml, 1.2mmol) were treated as described in Example 92 to give the title compound 212 mg, (38%). NMR: 1.50 (quin, 2H), 2.70 (q, 2H), 2.98 (dd, 2 H), 4.98 (s, 2H), 7.12-7.15 (m, 4H), 7.18 (t, 2H), 7.19 (t, 1H), 7.75 (d, 2H), 7.79 (d, 1H), 7.90 (d, 2H), 8.50 (d, 1H), 8.60 (s, 1H); m/z: 558 $[MH]^+$.

Example 94

2-[4-(2-Diethylaminoethoxy)anilino]-4-(6-phenylimidazo[1,2a]pyrid-3-yl)pyrimidine

3-(3-Dimethylaminoprop-2-en-1-oyl)-6-phenylimidazo[1,2a]pyridine (Method 38; 50mg, 0.17mmol) was added to a solution of 4-(2-diethylaminoethoxy)phenylguanidine (Method 42; 60mg, 0.19mmol) and sodium methoxide (11mg, 0.21mmol) in *n*-butanol (1.5ml) and the mixture was heated at 115°C for 15 hours. The volatiles were removed by evaporation and the residue purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (80:20) to give the title compound (5mg, 6%). NMR: 1.07 (t, 6H), 2.64 (q, 4H), 2.92 (t, 2H), 4.10 (t, 2H), 6.98 (d, 2H), 7.08 (m, 2H), 7.15 (d, 1H), 7.37-7.60 (m, 4H), 7.70 (d, 2H), 7.92 (s, 1H), 8.30 (s, 1H), 8.35 (d, 1H), 9.80 (d, 1H); m/z: 479 $[MH]^+$.

Example 95

4-(6-Methoxy-2-methylimidazo[1,2a]pyrid-3-yl)-2-(4-sulphamoylanilino)pyrimidine

3-(3-Dimethylaminoprop-2-en-1-oyl)-2-methyl-6-methoxyimidazo[1,2a]pyridine (Method 39; 862mg, 3.51mmol) was added to a solution of 4-sulphamoylphenylguanidine (Method 41; 1.5g, 7.0mmol) and sodium methoxide (758mg, 14mmol) in *N*-butanol (4ml) and the mixture was heated at reflux for 24 hours. The mixture was allowed to cool and the resulting precipitate collected by filtration and purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to ethyl acetate/methanol (90:10) to give the title compound. NMR: 2.60 (s, 3H), 3.88 (s, 3H), 6.70 (dd, 1H), 7.03 (d, 1H), 7.12 (d, 1H), 7.18 (s, 2H), 7.75 (d, 2H), 7.90 (d, 2H), 8.52 (d, 1H), 9.68 (d, 1H), 9.97 (s, 1H); m/z: 411 $[MH]^+$.

Example 96

2-(3-Chloroanilino)-4-(pyrazolo[2,3a]pyrid-3-yl)pyrimidine

Dry *n*-butanol (6.0ml) was added to a mixture of 3-(3-dimethylaminoprop-2-en-1-oyl)-2-methylpyrazolo[2,3a]pyridine (Method 18; 180mg, 0.84mmol), 3-chlorophenylguanidine (142mg, 0.84mmol) and sodium hydride (67mg of a 60% dispersion in mineral oil, 1.67mmol) and the mixture was heated under nitrogen at 125°C for 7 hours. The volatiles were removed by evaporation and the residue was triturated with a mixture of ether and distilled water. The precipitated solid was collected by filtration, washed with ether and distilled water and dried to give the title compound (78mg, 29%). NMR: 7.00 (d, 1H), 7.10 (t, 1H), 7.35 (m, 2H), 7.50 (t, 1H), 7.60 (d, 2H), 8.08 (s, 1H), 8.43 (d, 1H), 8.70 (d, 1H), 8.82 (d, 2H), 9.68 (s, 1H); m/z: 322 $[MH]^+$.

Example 97

2-Anilino-5-bromo-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

2-Amino-5-bromo-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Method 31; 200mg, 0.67mmol) and bromobenzene (0.08ml, 0.76mmol) were treated as described in Example 71 and the product was purified by chromatography eluting with hexane/ethyl acetate (50:50) increasing in polarity to (0:100) to give the title compound. NMR: 6.98-7.10 (m, 2H), 7.30 (dd, 2H), 7.50 (dd, 1H), 7.66 (d, 2H), 7.78 (d, 1H), 8.64 (s, 2H), 8.72 (s, 1H), 9.01 (d, 1H), 9.82 (s, 1H).

Example 98

2-Anilino-4-(5-bromoimidazo[1,2a]pyrid-3-yl)pyrimidine

2-Amino-4-(5-bromoimidazo[1,2a]pyrid-3-yl)pyrimidine (Method 35; 1.0g, 3.4mmol), and bromobenzene (4.36ml, 4.1mmol) were treated as described in Example 71 and the product purified by chromatography eluting with ethyl acetate/methanol (98:2) increasing in polarity to (90:10) to give the title compound 70mg (6%) NMR: 7.00 (dd, 1H), 7.30-7.40 (m, 4H), 7.59 (d, 1H), 7.65-7.75 (m, 3H), 8.42 (d, 1H), 8.60 (s, 1H), 9.70 (s, 1H); m/z: 364 $[M-H]^-$.

Preparation of Starting Materials

The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

Method 1

4-(2-Methylimidazo[1,2a]pyrid-3-yl)-2-methylthiopyrimidine

A mixture of 3-(3-dimethylaminoprop-2-en-1-oyl)-2-methylimidazo[1,2a]pyridine (Method 2) (20g, 87mmol), thiourea (6.52g, 86mmol) and sodium methoxide (1.19g, 22mmol) in butanol (220ml) was heated at 85°C for two hours under nitrogen. Methyl iodide (2ml, 32mmol) was added and the mixture heated at 85°C for a further 1 hour. Methanol was added and the volatiles were removed by evaporation. The residue was purified by chromatography eluting with ethyl acetate/methanol (100:0 increasing in polarity to 97:3) to give the title compound (16g, 71%). NMR: 2.59 (s, 1H), 2.62 (s, 3H), 7.10 (dd, 1H), 7.40 (dd, 1H), 7.42 (d, 1H), 7.63 (d, 1H), 8.62 (s, 1H), 9.54 (d, 1H), m/z: 257 $[MH]^+$.

Method 2

3-(3-Dimethylaminoprop-2-en-1-oyl)-2-methylimidazo[1,2a]pyridine

A mixture of 3-acetyl-2-methylimidazo[1,2a]pyridine (Method 3) (40g, 0.23mol) and DMFDMA (200ml) was heated at reflux under nitrogen for 4 days. The volatiles were removed by evaporation, the residue was triturated with hot ether and the solid product collected by filtration to give the title compound (21g, 40%). NMR: 2.64 (s, 3H), 3.29 (s, 6H),

5.50 (d, 1H), 7.00 (dd, 1H), 7.38 (dd, 1H), 7.54 (d, 1H), 7.70 (d, 1H), 9.55 (d, 1H), m/z: 230 $[MH]^+$.

Method 3

3-Acetyl-2-methylimidazo[1,2a]pyridine

A mixture of 2-aminopyridine (60g, 0.64mol) and 3-chloro-2,4-pentanedione (101.4g, 0.75mol) in ether (450ml) and THF (750ml) were heated at reflux for 12 hours, then left to stand at ambient temperature for 18 hours. The solvent was removed by evaporation and the residue was purified by chromatography eluting with dichloromethane/hexane (1:1) increasing in polarity to dichloromethane /methanol (98:2). The purified product was triturated with hexane to give the title compound (46.2g, 40%). NMR: 2.55 (s, 3H), 2.68 (s, 3H), 7.15 (dd, 1H), 7.56 (dd, 1H), 7.64 (d, 1H), 9.58 (d, 1H), m/z: 175 $[MH]^+$.

Method 4

4-(Imidazo[1,2a]pyrid-3-yl)-2-methylthiopyrimidine

A mixture of 3-(3-dimethylaminoprop-2-en-1-oyl)imidazo[1,2a]pyridine (Method 5) (0.90g, 4.2mmol), thiourea (0.32g, 4.2mmol) and sodium methoxide (0.34g, 6.3mmol) was heated at 85°C in *N*-butanol (10ml) for 2 hours. The mixture was allowed to cool to 30°C, methyl iodide (0.6ml, 9.6mmol) was added dropwise and stirring continued for a further 3 hours. The volatiles were removed by evaporation and the residue purified by chromatography, eluting with ethyl acetate/methanol (100:0 increasing in polarity to 97:3) to give the title compound (0.94g, 93 %). NMR: 2.61 (s, 3H), 7.22 (dd, 1H), 7.54 (dd, 1H), 7.72 (d, 1H), 7.77 (d, 1H), 8.56 (d, 1H), 8.66 (s, 1H), 9.83 (d, 1H); m/z: 243 $[MH]^+$.

Method 5

3-(3-Dimethylaminoprop-2-en-1-oyl)imidazo[1,2a]pyridine

A mixture of crude 3-acetylimidazo[1,2,a]pyridine (Method 6) (3.3g, 19.1mmol) and DMFDMA (40ml) was heated at reflux for 60 hours. The mixture was allowed to cool, the volatiles were removed by evaporation and the residue triturated with hot ether. The solid product was collected by filtration to give the title compound 2.29g, 52%. NMR: 2.90 (br s, 3H), 3.10 (br s, 3H), 5.81 (d, 1H), 7.09 (dd, 1H), 7.42 (dd, 1H), 7.65 (d, 1H), 7.70 (d, 1H), 8.43 (s, 1H), 9.72 (d, 1H); m/z: 216 $[MH]^+$.

Method 6

3-Acetylimidazo[1,2a]pyridine

Aluminium chloride (20.4g, 153.2mmol) was added in small portions to a solution of imidazo[1,2a]pyridine (8.9g, 75.7mmol) in dichloromethane (150ml) cooled at 5°C. The mixture was then allowed to warm to ambient temperature and stirred for 1 hour and then heated to reflux. Acetic anhydride (5.1ml, 53.9mmol) was then added slowly over 30 minutes and the mixture heated at reflux for further 90 minutes. The mixture was allowed to cool, the solvent was removed by evaporation and ice/water added to the residue. The aqueous mixture was made alkaline with 2M aqueous sodium hydroxide solution and extracted with ethyl acetate. The combined extracts were dried and the volatiles removed by evaporation to give a brown oil. This oil was shown to consist of ~35% of the title compound, the remainder being imidazo[1,2,a]pyridine. This mixture was used without further purification. NMR: 2.57 (s, 3H), 7.22 (dd, 1H), 7.61 (dd, 1H), 7.79 (d, 1H), 8.60 (s, 1H), 9.52 (d, 1H).

Method 7

4-(3,5-Dioxapiperidin-1-yl)sulphonylaniline

A mixture of 1-(3,5-dioxapiperidin-1-yl)sulphonyl-4-nitrobenzene (Method 8) (500mg, 1.82mmol) and 10% palladium on charcoal catalyst (150mg) in ethanol (25ml) and ethyl acetate (25ml) was stirred under an atmosphere of hydrogen for 3 hours. The catalyst was removed by filtration through diatomaceous earth and the filter pad was washed with ethanol and ethyl acetate. The volatiles were removed from the filtrate by evaporation and the residue triturated with ether and hexane to give the title compound (395mg, 88%). NMR: 4.90 (s, 2H), 5.10 (s, 4H), 6.02 (s, 2H), 6.58 (d, 2H), 7.50 (d, 2H).

Method 8

1-(3,5-Dioxapiperidin-1-yl)sulphonyl-4-nitrobenzene

4-Nitrobenzenesulphonamide (2.02g, 10mmol) was added to a solution of 1,3,5-trioxane (1.96g, 20mmol) in acetic acid (5ml). The mixture was stirred for 5 minutes and methanesulphonic acid (10ml) was added slowly. The mixture was then stirred at 35°C for 20 minutes, cooled to 0°C, diluted with water and extracted with ethyl acetate. The combined extracts were washed twice with water and twice with 5% aqueous sodium hydrogen carbonate solution, then dried and the volatiles removed by evaporation. The residue

was recrystallized from ethanol to give the title compound (955mg, 35%). NMR: 4.87 (s, 2H), 5.30 (s, 4H), 8.20 (d, 2H), 8.42 (d, 2H).

Method 9

4-(2-Diethylaminoethoxy)aniline

A mixture of 4-(2-diethylaminoethoxy)-1-nitrobenzene (Method 10) (1.0g, 4.2mmol) and 10% palladium on charcoal catalyst (200mg) in ethanol (30ml) was stirred under an atmosphere of hydrogen for 3 hours. The catalyst was removed by filtration through diatomaceous earth and the filter pad was washed with methanol. The volatiles were removed from the filtrate by evaporation to give the title compound (400mg, 46%) as an oil. M/z: 209 $[MH]^+$.

Method 10

4-(2-Diethylaminoethoxy)-1-nitrobenzene

Water (8ml) and xylene (35ml) were added to a mixture of sodium 4-nitrophenoxide (10.5g, 65mmol), 2-(diethylamino)ethylchloride hydrochloride (8.6g, 50mmol) and potassium carbonate (10.4g, 75mmol) and the resulting mixture was heated at reflux for 2 hours. A Dean-Stark apparatus was then fitted and the water was removed. The organic solution was allowed to cool to ambient temperature and left to stand for 18 hours. The solution was decanted from the precipitated solid and the volatiles were removed from the decanted solution by evaporation to give the title compound (8.0g, 52%) as an oil. NMR: 0.90 (t, 6H), 2.50 (q, 2H), 2.89 (t, 2H), 4.15 (t, 2H), 7.15 (d, 2H), 8.18 (d, 2H); m/z: 239 $[MH]^+$.

Method 11

4-[3-(*N*,*N*-Dimethyl)amino-2-hydroxypropoxy]aniline

3-*N*,*N*-Dimethylamino-2-hydroxy-3-(4-nitrophenoxy)propane (Method 12) (3.75 g) was dissolved in ethanol (40 ml). Under an atmosphere of nitrogen, 10% palladium-on-carbon (0.4g) was added. The nitrogen atmosphere was replaced by one of hydrogen and the reaction mixture was stirred overnight. The catalyst was removed by filtration through diatomaceous earth and the filtrate was evaporated to dryness. The residue was dissolved in diethyl ether containing a small amount of isopropanol and hydrogen chloride solution (1M in ether, 16 ml) was added. The ether was evaporated and the solid residue was suspended in isopropanol. This mixture was heated on a steam bath for several minutes then allowed to cool to ambient

temperature. The resulting powder was collected by filtration, washed with isopropanol, ether and dried (3.04 g 72.4%). NMR: 2.80 (s, 6H), 3.15 (m, 2H), 3.88 (m, 2H), 4.25 (m, 1H), 5.93 (br S, 1H), 6.88 (m, 4H); m/z 211 $[MH]^+$; EA $C_{11}H_{18}N_2O_2$..1.6 HCl requires C; 49.2, H; 7.4, N; 10.4, Cl; 21.7%: found: C; 49.2, H; 7.2, N; 10.1; Cl; 19.1%.

Method 12

3-*N*,*N*-Dimethylamino-2-hydroxy-1-(4-nitrophenoxy)propane

1-(4-Nitrophenoxy)-2,3-epoxypropane (Method 13) (4.3 g) was dissolved in methanol (30 ml) and DMF (10 ml). Dimethylamine (2M solution in methanol, 17 ml) was added and the mixture was stirred at ambient temperature overnight. The reaction mixture was evaporated to dryness and the residue was dissolved in saturated sodium bicarbonate solution and ethyl acetate. The ethyl acetate layer was separated and washed twice with saturated brine, dried over anhydrous sodium sulphate, filtered and evaporated to yield an oil that slowly crystallised under high vacuum (4.79g, 89.9%). NMR ($CDCl_3$): 2.33 (s, 6H), 2.98 (m, 1H), 2.54 (m, 1H), 4.00 (m, 3 H), 7.00 (d, 2H), 8.20 (d, 2H); m/z 241 $[MH]^+$.

Method 13

1-(4-Nitrophenoxy)-2,3-epoxypropane

1-(4-Nitrophenoxy)-2,3-epoxypropane was prepared by an analogous method to that described by Zhen-Zhong Lui *et. al.* in Synthetic Communications (1994), *24*, 833-838.

4-Nitrophenol (4.0 g), anhydrous potassium carbonate (8.0 g) and tetrabutylammonium bromide (0.4 g) were mixed with epibromohydrin (10 ml). The reaction mixture was heated at 100°C for 1 hour. After cooling to ambient temperature, the reaction mixture was diluted with ethyl acetate and filtered. The filtrate was evaporated to dryness and the residue was co-distilled twice with toluene. The resulting oil was purified by column chromatography and eluted with ethanol (1.0%):dichloromethane to yield on evaporation an oil that crystallised (4.36 g, 77.7%). NMR ($CDCl_3$): 2.78 (m, 1H), 2.95 (m, 1H), 3.38 (m, 1H), 4.02 (dd, 1 H), 4.38 (dd, 1H), 7.00 (d, 2H), 8.20 (d, 2H); m/z 196 $[MH]^+$.

Method 14

2-Methylthio-4-(2,5-dimethylimidazo[1,2a]pyrid-3-yl)pyrimidine

A mixture of 3-(3-dimethylaminoprop-2-en-1-oyl)-2,5-dimethylimidazo[1,2a]pyridine (Method 15) (3.50g, 14.4mmol), thiourea (1.09g, 14.4mmol) and sodium methoxide (1.01g, 18.7mmol) were heated at 85°C in 1-butanol (50ml) for 2 hours. The mixture was allowed to cool to 30°C and methyl iodide (1.8ml, 28.8mmol) was added dropwise and the mixture stirred for a further 3 hours. The volatiles were removed by evaporation and the residue purified by chromatography eluting with ethyl acetate/methanol (100:0 increasing in polarity to 97:3) to give the title compound (2.37g, 61%). NMR: 2.41 (s, 3H), 2.60 (s, 3H), 2.70 (s, 3H), 7.56 (d, 1H), 7.88 (d, 1H), 7.92 (d, 1H), 8.81 (d, 1H), 9.39 (s, 1H); m/z: 271 $[MH]^+$.

Method 15

3-(3-Dimethylaminoprop-2-en-1-oyl)-2,5-dimethylimidazo[1,2a]pyridine

A solution of 3-acetyl-2,5-dimethylimidazo[1,2,a]pyridine (Method 16) (3.60g, 19.1 mmol) in DMFDMA (20ml) was heated at reflux for 60 hours. The mixture was allowed to cool and the solvent was removed by evaporation. The residue was triturated with hot ether, the solid collected by filtration and dried to give the title compound (3.61g, 84%). NMR: 2.30 (s, 3H), 2.62 (s, 3H), 2.90 (br s, 3H), 3.10 (br s, 3H), 5.48 (d, 1H), 7.22 (dd, 1H), 7.44 (d, 1H), 7.68 (d, 1H), 9.39 (dd, 1H).

Method 16

3-Acetyl-2,5-dimethylimidazo[1,2a]pyridine

3-Chloro-2,4-pentanedione (6.5ml, 54.4mmol) was added to a suspension of 2-amino-4-methylpyridine (5.00g, 46.3mmol) and sodium iodide (10mg) in THF (60ml) and the mixture was heated at reflux for 16 hours. The reaction mixture was allowed to cool and the solvent was removed by evaporation. The resulting solid residue was triturated with hot hexane, collected by filtration and dried to give the title compound (3.69g, 43%). NMR: 2.35 (s, 3H), 2.75 (s, 3H), 7.41 (dd, 1H), 7.57 (d, 1H), 9.40 (d, 1H); m/z: 189 $[MH]^+$.

Method 17

4-(2-Methylpyrazolo[2,3a]pyrid-3-yl)-2-methylthiopyrimidine

A mixture of 3-(3-dimethylaminoprop-2-en-1-oyl)-2-methyl-pyrazolo[2,3a]pyridine (Method 18) (3.89g, 17mmol), thiourea (1.27g, 17mmol) and sodium methoxide (0.929g, 17mmol) in butanol (45ml) was heated at 85°C for two hours under nitrogen. Methyl iodide (1.05ml, 17mmol) was added and the mixture heated at 85°C for a further 2 hours. The volatiles were removed by evaporation and the residue was purified by chromatography eluting with ethyl acetate/methanol (100:0 increasing in polarity to 97:3) to give the title compound (3.1g, 68%). NMR: 2.58 (s, 1H), 2.68 (s, 3H), 7.04 (dd, 1H), 7.39 (dd, 1H), 7.48 (d, 1H), 8.35 (d, 1H), 8.50 (d, 1H), 8.72 (d, 1H); m/z: 257 $[MH]^+$.

Method 18

3-(3-Dimethylaminoprop-2-en-1-oyl)-2-methylpyrazolo[2,3a]pyridine

A mixture of 3-acetyl-2-methylpyrazolo[2,3a]pyridine (Method 19) (2g, 11.5mmol) and DMFDMA (10ml) was heated 110°C under nitrogen for 48 hours. The volatiles were removed by evaporation, the residue was triturated with hot ether and the solid product collected by filtration to give the title compound (1.98g, 75%). NMR: 2.60 (s, 3H), 3.30 (s, 6H), 5.49 (d, 1H), 6.95 (dd, 1H), 7.38 (dd, 1H), 7.62 (d, 1H), 8.10 (d, 1H), 8.62 (d, 1H); m/z: 230 $[MH]^+$.

Method 19

3-Acetyl-2-methylpyrazolo[2,3a]pyridine

Potassium carbonate (53.8g, 0.39mol) and then 2,4-pentanedione (24.8g, 0.25mol) were added to a solution of 1-aminopyridinium iodide (26.9g, 0.12mol) in water (336ml) and the mixture was heated at 80°C for 2 hours, allowed to cool to ambient temperature and left to stand for 18 hours. Water was added and the mixture was extracted to with ethyl acetate. The combined extracts were dried and the volatiles were removed by evaporation. The residue was recrystallized from hot hexane and the product collected by filtration. Solvent was removed from the filtrate by evaporation and was added to the insoluble residue from the recrystallization. This crude mixture was purified by chromatography eluting with dichloromethane/hexane (1:1) increasing in polarity to dichloromethane/methanol (97:3). This product was triturated with hexane and added to the product obtained from the initial

recrystallization to give the title compound (9.6g, 33%). NMR: 2.50 (s, 3H), 2.62 (s, 3H), 7.09 (dd, 1H), 7.55 (dd, 1H), 8.12 (d, 1H), 8.72 (d, 1H); m/z: 175 $[MH]^+$.

Method 20

2-Chloro-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

A suspension of 2-hydroxy-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Method 21; 9.92g, 46%) in phosphoryl chloride (200ml) and phosphorus pentachloride (11g, 53%) was heated at reflux under nitrogen for 24 hours. Excess phosphoryl chloride was removed by evaporation, ice water was added and the mixture neutralised with 2M aqueous sodium hydroxide solution. The aqueous mixture was extracted with ethyl acetate, dried and evaporated to give the title compound 7.42g (69%). NMR: 7.15 (dd, 1H), 7.59 (dd, 1H), 7.80 (d, 1H), 8.05 (d, 1H), 8.64 (d, 1H), 8.79 (s, 1H), 9.72 (d, 1H); m/z: 231 $[MH]^+$.

Method 21

2-Hydroxy-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

A solution of sodium nitrate (11.04g, 0.16mol) in water (100ml) was added to a solution of 2-amino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine (Method 22; 11.27g, 0.053mol) in 70% acetic acid (330ml) at 60°C. The mixture was heated at 60°C for 3 hours, allowed to cool and neutralised with 5M aqueous sodium hydroxide solution, the resulting precipitate was collected by filtration, washed quickly with cold water and dried in vacuum oven at 50°C to give the title compound 9.95g (89%). NMR: 6.98 (d, 1H), 7.12 (dd, 1H), 7.55 (dd, 1H), 7.80 (d, 1H), 7.82 (d, 1H), 8.70 (s, 1H); m/z: 213 $[MH]^+$.

Method 22

2-Amino-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

A mixture of 3-(3-dimethylaminoprop-2-en-1-oyl)imidazo[1,2a]pyridine (Method 5; 20g, 0.093mol), sodium methoxide (20.1g, 0.372mol) and guanidine hydrochloride (22.09g, 0.233mol) in *n*-butanol (1500ml) and methanol (1000ml) were heated at reflux for 60 hours. The resulting solution was decanted from insoluble material, the volatiles were removed by evaporation and the residue was purified by chromatography eluting with dichloromethane / methanol (97:3) to give the title compound 13g (67%). NMR: 6.78 (s, 1H), 7.15-7.05 (m, 2H), 7.45 (dd, 2H), 7.70 (d, 1H), 8.20 (d, 1H), 8.50 (s, 1H), 10.15 (d, 1H); m/z: 212 $[MH]^+$.

Method 23

4-(*N*-Methylsulphamoyl)aniline

Methylamine (3ml of a 33% solution in ethanol) and then triethylamine (0.159ml, 1.1mmol) was added to sulphanilyl fluoride (200mg, 1.1mmol), and the mixture heated at 80°C for 6 hours then at ambient temperature for 18 hours. The volatiles were removed by evaporation and the residue azeotroped with toluene to give the title compound (160mg, 76%). NMR: 2.30 (s, 3H), 5.85 (s, 2H), 6.60 (d, 2H), 7.39 (d, 2H); m/z: 187 $[MH]^+$.

Method 24

4-[*N*-(2-Methoxyethyl)sulphamoyl]aniline

A mixture of 2-methoxyethylamine (859mg, 11.4mmol), sulphanilyl fluoride (1.0g, 5.71mmol), and triethylamine (1.72g, 22.9mmol) in *n*-butanol (15ml) was heated at reflux for 18 hours. The mixture was allowed to cool and the volatiles were removed by evaporation. The residue was purified by chromatography eluting with ethyl acetate / hexane (50:50) increasing in polarity to (70:30) to give the title compound (860mg, 65%). NMR: 2.78 (q, 2H), 3.15 (s, 3H), 3.25 (t, 2H), 5.87 (s, 2H), 6.58 (d, 2H), 7.10 (t, 1H), 7.40 (d, 2H); m/z: 231 $[MH]^+$.

Method 25-26

The following compounds were prepared using the procedure of Method 24.

Meth	Compound Name	NMR	m/z
25	4-(*N*-Propylsulphamoyl)aniline	0.78 (t, 3H), 1.40 -1.25 (m, 2H), 2.60 (q, 2H), 5.84 (s, 2H), 6.59 (d, 2H), 7.00 (t, 1H), 7.39 (d, 2H)	
26	4-(*N*-Cyclopropylsulphamoyl) aniline	0.01-0.15 (m, 4H), 1.70-1.75 (m, 1H), 5.60 (s, 2H), 6.30 (d, 2H), 7.05 (s, 1H), 7.10 (d, 2H)	211 [M-H]-

Method 27

1-[3-(4-Bromobenzoylamino)propyl]imidazole

1-(3-Aminopropyl)imidazole (2.39ml, 0.02mol) was added to a solution of 4-bromobenzoyl chloride (4.0g, 0.018mol) in ethanol (250ml). The mixture was stirred at ambient temperature for 18 hours. The volatiles were removed by evaporation and the residue was purified by chromatography eluting with hexane / dichloromethane (50:50) increasing in polarity to dichloromethane / methanol (80:20) to give the title compound. NMR: 1.95 (m, 2H), 3.20 (q, 2H), 4.0 (t, 2H), 6.87 (s, 1H), 7.19 (s, 1H), 7.64 (d, 2H), 7.68 (s, 1H), 7.78 (d, 2H), 8.58 (t, 1H); m/z: 308 $[MH]^+$.

Method 28

1-[3-(4-Bromobenzoylamino)propyl]-2-oxopyrolidine

1-(3-Aminopropyl)-2-oxopyrolidine (3.07ml 14mmol) was treated as described in Method 27 to give the title compound. NMR: 1.68 (quin, 2H), 1.90 (quin, 2H), 2.0 (t, 2H), 3.15-3.22 (m, 4H), 3.29-3.33 (m, 2H), 7.64 (d, 2H), 7.78 (d, 2H), 8.48 (t, 1H).

Method 29

2,4-Dichloro-1-(2-methoxyethylsulphamoyl)benzene

2,4-Dichlorobenzenesulphonyl chloride (500mg 2.1mmol) and 2-methoxyethylamine (230mg, 3.1mmol) in *n*-butanol (10ml) was heated at reflux for one hour. The volatiles were removed by evaporation and residue purified by chromatography eluting with hexane/ethyl acetate (50:50) to give the title compound. NMR: 3.04 (t, 2H), 3.08 (s, 3H), 3.22 (t, 2H), 7.60 (dd, 1H), 7.82 (d, 1H), 7.92 (d, 1H), 8.0 (s, 1H); m/z: 282 $[M-H]^-$.

Method 30

2,4-Dichloro-1-(1-propylsulphamoyl)benzene

2,4-Dichlorobenzenesulphonyl chloride (500mg 2.1mmol) and 1-propylamine (0.2ml, 2.4mmol) in *n*-butanol (10ml) was heated at reflux for 48 hours. The volatiles were removed by evaporation and the residue triturated with ether and the product collected by filtration to give the title compound. NMR: 0.78 (t, 3H), 1.35 (q, 2H), 2.79 (t, 2H), 7.60 (dd, 1H), 7.84 (d, 1H), 7.92 (d, 2H).

Method 31

2-Amino-5-bromo-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine

Bromine (54ml, 0.0011mol) was added dropwise to a solution of 2-amino-4-(imidazo [1,2a]pyrid-3-yl)pyrimidine (Method 22; 200mg, 0.95mmol) in acetic acid (4ml) at ambient temperature. The mixture was heated at 65°C for 90 minutes and allowed to cool. The resulting precipitate was collected by filtration, washed with hexane and dried to give the title compound. NMR: 7.44 (dd, 1H), 7.90-8.00 (m, 2H), 8.59 (s, 1H), 8.99 (s, 1H), 9.78 (d, 1H); m/z: 290 $[MH]^+$.

Method 32

5-Bromoimidazo[1,2a]pyridine

A solution of bromoacetaldehyde diethylacetyl (50ml, 0.332mol) in dioxane (143ml), water (85ml) and conc. hydrochloric acid (5ml) was heated at reflux for 30 minutes and the mixture allowed to cool. Sodium hydrogen carbonate (53g) was added followed by a solution of 5-bromo-2-aminopyridine (30g, 0.174mol) in dioxane (230ml) and water (85ml) and the mixture was heated at reflux for 24 hours. The mixture was allowed to cool, poured into water and acidified with 2M hydrochloric acid. The mixture was washed with ethyl acetate and the aqueous layer was basified with 2M aqueous sodium hydroxide solution. The aqueous mixture was extracted with ethyl acetate. The extracts were combined, dried and the volatiles removed by evaporation. The residue was purified by chromatography eluting with hexane/ethyl acetate (50:50) in creasing in polarity to (25:50) to give the title compound 20g (59%). NMR: 7.30 (dd, 1H), 7.54 (d, 1H), 7.59 (s, 1H), 7.90 (s, 1H), 8.89 (s, 1H); m/z: 197 $[MH]^+$.

Method 33

3-Acetyl-5-bromoimidazo[1,2a]pyridine

Aluminium chloride (10.2g, 77mmol) was added in portions over 10 minutes to a solution of 5-bromoimidazo[1,2a]pyridine (Method 32; 5.0g, 26mmol) in dichloromethane (100ml) cooled to 0°C. The mixture was heated to reflux and acetyl chloride (2.54ml, 36mmol) was added over 15 minutes. The mixture was heated at reflux for 24 hours, cooled to 0°C, and further aluminium chloride (10.2g, 77mmol) followed by acetyl chloride (3.26ml) were added. The mixture heated at reflux for 24 hours and then the volatiles were removed by evaporation. Iced water was added, the mixture was basified with 2M aqueous sodium hydroxide solution and extracted with ethyl acetate. The extracts were washed with water, dried and the solvent evaporated to the title compound which was used without further

purification 4.0g. NMR: 2.58 (s, 3H), 7.74-7.82 (m, 2H), 8.62 (s, 1H), 9.62 (s, 1H); m/z: 241 $[MH]^+$

Method 34

5-Bromo-3-(3-dimethylaminoprop-2-en-1-oyl)imidazo[1,2a]pyridine

3-Acetyl-5-bromoimidazo[1,2a]pyridine (Method 33; 4.0g) was dissolved in DMFDMA (200ml) and the mixture was heated at reflux under nitrogen for 72 hours. The excess DMFDMA was removed by evaporation and the residue triturated with hot ether, collected by filtration and washed with ether to give the title compound 2.6g (53%). NMR: 2.90 (s, 3H), 3.12 (s, 1H), 5.82 (d, 1H), 7.58 (dd, 1H), 7.64 (d, 1H), 7.70 (s, 1H), 8.44 (s, 1H), 9.90 (s, 1H); m/z: 294 $[MH]^+$.

Method 35

2-Amino-4-(5-bromoimidazo[1,2a]pyrid-3-yl)pyrimidine

A mixture of 5-bromo-3-(3-dimethylaminoprop-2-en-1-oyl)imidazo[1,2a]pyridine (Method 34; 2.5g, 8.5mmol) guanidine hydrochloride (2.01g, 21mmol) and sodium methoxide (1.83g, 34mmol) in *n*-butanol (140ml) and methanol (45ml) was heated at reflux for 18 hours. The volatiles were removed by evaporation and the residue purified by chromatography eluting with dichloromethane/methanol (95:5) to give the title compound 1.1g (45%). NMR: 6.86 (s, 2H), 7.12 (d, 1H), 7.57 (dd, 1H), 7.68 (d, 1H), 8.22 (d, 1H), 8.51 (s, 1H); m/z: 290 $[MH]^+$.

Method 36

6-Phenylimidazo[1,2a]pyridine

2-Amino-4-phenylpyridine (0.90g, 5.29mmol) was treated as described in Method 32 to give the title compound. NMR: 7.07 (d, 1H), 7.35-7.53 (m, 4H), 7.59 (s, 1H), 7.64 (d, 2H), 7.83 (s, 1H), 8.18 (d, 1H); m/z: 195 $[MH]^+$.

Method 37

3-Bromo-6-phenylimidazo[1,2a]pyridine

A solution of bromine (0.24ml, 4.6mmol) in water (10ml) was added to a solution of 6-phenylimidazo[1,2a]pyridine (Method 36; 0.85g, 4.88mmol) in ethanol (15ml) and the

mixture stirred for 14 hours in the dark. The mixture was basified with aqueous sodium hydrogen carbonate solution and extracted with dichloromethane. The extracts were dried, the solvent removed by evaporation and the residue triturated with ether an collected by filtration to give the title compound. NMR: 7.38-7.56 (m, 4H), 7.77 (s, 1H), 7.83 (d, 2H), 7.96 (s, 1H), 8.39 (d, 1H); m/z: 273 $[MH]^+$.

Method 38

3-(3-Dimethylaminoprop-2-en-1-oyl)-6-phenylimidazo[1,2a]pyridine

Phenylmagnesium bromide (2.7ml of a 1M solution in THF) was added to a solution of 3-bromo-6-phenylimidazo[1,2a]pyridine (Method 37; 0.48g, 1.76mmol) in THF under nitrogen and the mixture was heated at reflux for 2 hours. The mixture was cooled to 0°C and *N*-methoxy-*N*-methylacetamide (0.3ml 2.64mmol) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 18 hours. The reaction mixture was diluted with ether washed with aqueous sodium hydrogen carbonate solution, then brine dried and the volatiles removed by evaporation. The residue was dissolved in DMFDMA (10ml) and the mixture heated at reflux under nitrogen for 60 hours. The excess DMFDMA was removed by evaporation and the residue triturated with hot ether, collected by filtration and washed with ether to give the title compound 170mg (33%). NMR: 2.8-3.2 (br d, 6H), 5.85 (d, 1H), 7.38-7.58 (m, 4H), 7.67 (d, 1H), 7.86 (d, 2H), 8.00 (s, 1H), 8.48 (s, 1H), 9.76 (d, 1H); m/z: 292 $[MH]^+$.

Method 39

3-(3-Dimethylaminoprop-2-en-1-oyl)-2-methyl-6-methoxyimidazo[1,2a]pyridine

3-Acetyl-6-methoxy-2-methylimidazo[1,2a]pyridine (Method 40; 1.49g, 7.3mmol) and toluenesulphonic acid (5mg) in DMFDMA (25ml) was heated at reflux for 20 hours. The excess DMFDMA was removed by evaporation. The residue was triturated with ether and the product collected by filtration to give the title compound. NMR: 2.69 (s, 3H), 3.28 (s, 6H), 3.82 (s, 3H), 5.44 (d, 1H), 6.69 (dd, 1H), 6.97 (d, 1H), 7.65 (d, 1H), 9.21 (d, 1H); m/z: 260 $[MH]^+$.

Method 40

3-Acetyl-6-methoxy-2-methylimidazo[1,2a]pyridine

A solution of 3-chloroacetoacetone (2.86 ml) in THF (6ml) was added to a solution of 2-amino-4-methoxypyridine (2.71g, 21.8mmol) in THF (14ml) and the mixture was stirred at ambient temperature for 30 minutes and then heated at reflux for 3 hours. The solvent was removed by evaporation and the residue purified by chromatography eluting with dichloromethane/methanol (100:0) increasing in polarity to (97:3). The product was recrystallized from *tert*-butylmethyl ether to give the title compound (2.1g, 47%). NMR: 2.05 (s, 3H), 2.63 (s, 3H), 3.86 (s, 3H), 6.83 (dd, 1H), 7.07 (d, 1H), 9.20 (d, 1H); m/z: 205 $[MH]^+$.

Method 41

4-Sulphamoylphenylguanidine

A mixture of sulphanilamide (20g, 0.166mol), benzoyl cyanamide (34g, 0.33mol) in ethanol (60ml) and concentrated hydrochloric acid (11ml) was heated on a steam bath until the solvent had evaporated. Water was added and the mixture heated at reflux for 5 minutes. Sodium hydroxide (14.4g) was added and the mixture heated at reflux. The mixture was allowed to cool and was adjusted to pH2 with hydrochloric acid and the precipitated solid removed by filtration. The filtrate was neutralised and the solvent removed by evaporation. The residue was recrystallized from water to give crude title product. m/z: 215 $[MH]^+$.

Method 42

4-(2-Diethylaminoethoxy)phenylguanidine

A mixture of 3,5-dimethylpyrazolylformidinium nitrate (0.20g, 1mmol), 4-(2-diethylaminoethoxy)aniline (Method 9; 1.0g, 4.8mmol) in water (1ml) was heated at reflux for 3 hours. The solvent was removed by evaporation, the residue triturated with hot ether and the product collected by filtration to give crude title compound. NMR: 0.98 (t, 6H), 2.57 (q, 4H), 2.79 (t, 2H), 4.00 (t, 2H), 6.99 (d, 2H), 7.15 (d, 2H); m/z: 251 $[MH]^+$.

Example 99

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof (hereafter compound X), for therapeutic or prophylactic use in humans:-

(a): Tablet I	mg/tablet
Compound X	100
Lactose Ph.Eur	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v paste)	2.25
Magnesium stearate	3.0

(b): Tablet II	mg/tablet
Compound X	50
Lactose Ph.Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v paste)	2.25
Magnesium stearate	3.0

(c): Tablet III	mg/tablet
Compound X	1.0
Lactose Ph.Eur	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v paste)	0.75
Magnesium stearate	1.0

(d): Capsule	mg/capsule
Compound X	10
Lactose Ph.Eur	488.5
Magnesium stearate	1.5

(e): Injection I	(50 mg/ml)
Compound X	5.0% w/v
1M Sodium hydroxide solution	15.0% v/v
0.1M Hydrochloric acid	(to adjust pH to 7.6)

Polyethylene glycol 400	4.5% w/v
Water for injection	to 100%

(f): Injection II	**10 mg/ml**
Compound X	1.0% w/v
Sodium phosphate BP	3.6% w/v
0.1M Sodium hydroxide solution	15.0% v/v
Water for injection	to 100%

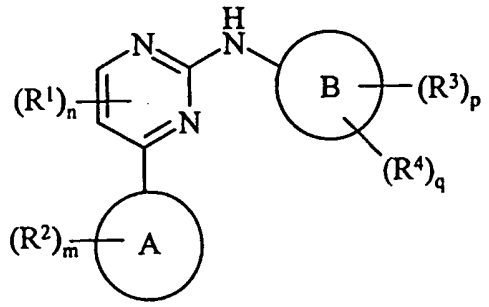
(g): Injection III	**(1mg/ml,buffered to pH6)**
Compound X	0.1% w/v
Sodium phosphate BP	2.26% w/v
Citric acid	0.38% w/v
Polyethylene glycol 400	3.5% w/v
Water for injection	to 100%

Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

CLAIMS

1. A compound of formula (I):



(I)

wherein:

Ring A is imidazo[1,2a]pyrid-3-yl or pyrazolo[2,3a]pyrid-3-yl;

R^2 is attached to a ring carbon and is selected from halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkylS(O)$_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, *N*-(C_{1-6}alkyl)sulphamoyl, *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl, phenyl, heterocyclic group, phenylthio or (heterocyclic group)thio; wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, phenyl or heterocyclic group may be optionally substituted on carbon by one or more G; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from Q;

m is 0-5; wherein the values of R^2 may be the same or different;

R^1 is halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-3}alkyl, C_{2-3}alkenyl, C_{2-3}alkynyl, C_{1-3}alkoxy, C_{1-3}alkanoyl, *N*-(C_{1-3}alkyl)amino, *N,N*-(C_{1-2}alkyl)$_2$amino, C_{1-3}alkanoylamino, *N*-(C_{1-3}alkyl)carbamoyl, *N,N*-(C_{1-2}alkyl)$_2$carbamoyl, C_{1-3}alkylS(O)$_a$ wherein a is 0 to 2, *N*-(C_{1-3}alkyl)sulphamoyl or *N,N*-(C_{1-3}alkyl)$_2$sulphamoyl; wherein any C_{1-2}alkyl, C_{1-3}alkyl, C_{2-3}alkenyl or C_{2-3}alkynyl may be optionally substituted on carbon by one or more J;

n is 0 to 2, wherein the values of R^1 may be the same or different;

Ring B is phenyl or phenyl fused to a C_{5-7}cycloalkyl ring;

R^3 is halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

p is 0-4; wherein the values of R^3 may be the same or different;

R^4 is a group A-E-; wherein

A is selected from C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl; which C_{1-6}alkyl, phenyl, a heterocyclic group, C_{3-8}cycloalkyl, phenylC_{1-6}alkyl, (heterocyclic group)C_{1-6}alkyl or C_{3-8}cycloalkylC_{1-6}cycloalkyl may be optionally substituted on carbon by one or more D; and wherein if said heterocyclic group contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R;

E is a direct bond or -O-, -C(O)-, -OC(O)-, -C(O)O-, -$N(R^a)$C(O)-, -C(O)$N(R^a)$-, -$N(R^a)$-, -$S(O)_r$-, -$SO_2N(R^a)$- or -$N(R^a)SO_2$-; wherein R^a is hydrogen or C_{1-6}alkyl optionally substituted by one or more D and r is 0-2;

D is independently selected from oxo, halo, nitro, cyano, hydroxy, trifluoromethyl, trifluoromethoxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkanoyloxy, *N*-(C_{1-6}alkyl)amino, *N,N*-(C_{1-6}alkyl)$_2$amino, C_{1-6}alkanoylamino, *N*-(C_{1-6}alkyl)carbamoyl, *N,N*-(C_{1-6}alkyl)$_2$carbamoyl, C_{1-6}alkyl$S(O)_a$ wherein a is 0 to 2, C_{1-6}alkoxycarbonyl, C_{1-6}alkoxycarbonylamino, benzyloxycarbonylamino, *N*-(C_{1-6}alkyl)sulphamoyl and *N,N*-(C_{1-6}alkyl)$_2$sulphamoyl; wherein any C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl or phenyl may be optionally substituted on carbon by one or more K;

q is 0-2; wherein the values of R^4 maybe the same or different; and wherein $p + q \leq 5$;

G, J and K are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; and

Q and R are independently selected from C_{1-4}alkyl, C_{1-4}alkanoyl, C_{1-4}alkylsulphonyl, C_{1-4}alkoxycarbonyl, carbamoyl, *N*-(C_{1-4}alkyl)carbamoyl, *N,N*-(C_{1-4}alkyl)carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

2. A compound of formula (I) according to claim 1 wherein R^1 is bromo or 2-hydroxyethylthio and n is 0-1;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

3. A compound of formula (I) according to any of claims 1 or 2 wherein Ring A is imidazo[1,2a]pyrid-3-yl;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

4. A compound of formula (I) according to any of claims 1 - 3 wherein R^2 is attached to a ring carbon and is selected from fluoro, chloro, bromo, cyano, methyl, methoxy, ethylthio, 2-hydroxyethylthio or 2-dimethylaminoethylthio and m is 0-2; wherein the values of R^2 may be the same or different;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

5. A compound of formula (I) according to any of claims 1 - 4 wherein R^3 is fluoro, chloro, bromo or sulphamoyl; and p is 1;
or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

6. A compound of formula (I) according to any of claims 1 - 5 wherein R^4 is methyl, ethyl, methoxy, methylthio, acetyl, benzyloxy, mesyl, *N,N*-diethylaminoethoxy, 3-*N,N*-dimethylamino-2-hydroxypropoxy, phenoxy, *N*-methylcarbamoyl, *N,N*-dimethylcarbamoyl, *N*-(3-imidazol-1-ylpropyl)carbamoyl, *N*-[3-(2-oxo-pyrrolidin-1-yl)propyl]carbamoyl, 3,5-dioxapiperidin-1-ylsulphonyl, *N*-cyclopropylsulphamoyl, *N*-cyclopropylmethylsulphamoyl, anilinosulphonyl, *N*-pyrimidin-2-ylsulphamoyl, *N*-methylsulphamoyl, *N*-propylsulphamoyl, *N*-(2-methoxyethyl)sulphamoyl, *N*-(2-methylaminoethyl)sulphamoyl, *N*-(2-isopropylaminoethyl)sulphamoyl, *N*-(2-dimethylaminoethyl)sulphamoyl, *N*-(2-diethylaminoethyl)sulphamoyl, *N*-[2-(hydroxyethylamino)ethyl]sulphamoyl, *N*-[2-(diethylaminoethyl)ethyl]sulphamoyl, *N*-(pyrrolidin-1-ylethyl)sulphamoyl, *N*-[2-(1-methylpyrrolidin-2-yl)ethyl]sulphamoyl, *N*-(2-piperidin-1-ylethyl)sulphamoyl, *N*-(2-piperazin-1-ylethyl)sulphamoyl, *N*-(2-morpholinoethyl)sulphamoyl,

N-(2-imidazol-4-ylethyl)sulphamoyl, *N*-(3-hydroxypropyl)sulphamoyl, *N*-(2,3-dihydroxypropyl)sulphamoyl, *N*-(3-methoxypropyl)sulphamoyl, *N*-(3-aminopropyl)sulphamoyl, *N*-(3-methylaminopropyl)sulphamoyl, *N*-(3-dimethylaminopropyl)sulphamoyl, *N*-(3-diethylaminopropyl)sulphamoyl, *N*-(3-isopropylaminopropyl)sulphamoyl, *N*-(3-*t*-butoxycarbonylaminopropyl)sulphamoyl, *N*-(3-benzyloxycarbonylaminopropyl)sulphamoyl, *N*-[3-(2-oxopyrrolidin-1-yl)propyl]sulphamoyl, *N*-(3-morpholinopropyl)sulphamoyl, *N*-[3-(4-methylpiperazin-1-yl)propyl]sulphamoyl, *N*-(3-imidazol-1-ylpropyl)sulphamoyl or *N*-(5-hydroxypentyl)sulphamoyl; and q is 1;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

7. A compound of formula (I) according to any of claims 1 - 6 wherein Ring B is phenyl; or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

8. A compound of formula (I) selected from:

2-(4-Sulphamoylanilino)-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine;

2-[4-(*N*-Methylsulphamoyl)anilino]-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine;

2-{4-[*N*-(2-Methoxyethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine;

2-{4-[*N*-(3-Methoxypropyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine;

2-{4-[*N*-(3-Isopropylaminopropyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine;

2-{4-[*N*-(3-Dimethylaminopropyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl) pyrimidine;

2-{4-[*N*-(2-Dimethylaminoethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine;

2-{4-[*N*-(2-Methylaminoethyl)sulphamoyl]anilino}-4-(imidazo[1,2a]pyrid-3-yl)pyrimidine; or

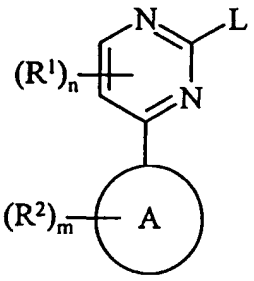
2-{4-[*N*-(2-Methoxyethyl)sulphamoyl]anilino}-4-[5-(2-hydroxyethylthio)imidazo[1,2a] pyrid-3-yl]pyrimidine;

or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof.

9. A process for preparing a compound of formula (I) according to claim 1, or a pharmaceutically acceptable salt or an *in vivo* hydrolysable ester thereof, which process

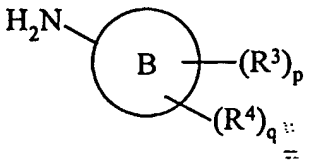
(wherein R^1, R^2, R^3, R^4, Ring A, Ring B, m, p, q and n are, unless otherwise specified, as defined in formula (I)) comprises of:

a) reaction of a pyrimidine of formula (II):



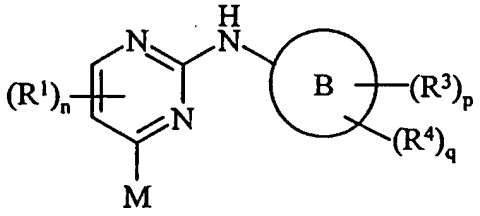
(II)

wherein L is a displaceable group; with an amine of formula (III):



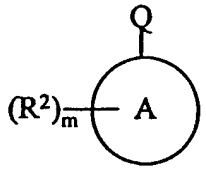
(III)

b) reacting a pyrimidine of formula (IV):



(IV)

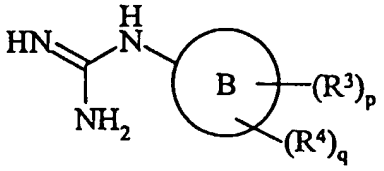
with a compound of the formula (V):



(V)

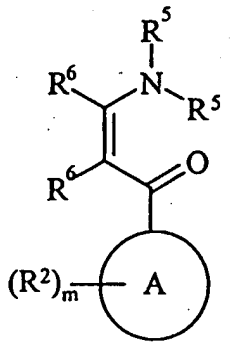
wherein one of M and Q is a displaceable group X and the other is an metallic reagent Y; or

c) reacting a compounds of formula (VI):



(VI)

with a compound of formula (VII):



(VII)

wherein R^5 is C_{1-6}alkyl and R^6 is hydrogen or R^1;

and thereafter if necessary:

i) converting a compound of the formula (I) into another compound of the formula (I);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

10. A pharmaceutical composition which comprises a compound of formula (I) according to any one of claims 1 - 8, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof in association with a pharmaceutically-acceptable diluent or carrier.

11. A compound of the formula (I) according to any one of claims 1 - 8, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof for use in a method of treatment of the human or animal body by therapy.

12. The use of a compound of the formula (I) according to any one of claims 1 - 8, or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, in the manufacture of a medicament for use in the treatment of cancers (solid tumours and leukemias), fibroproliferative and differentiative disorders, psoriasis, rheumatoid arthritis, Kaposi's sarcoma, haemangioma, acute and chronic nephropathies, atheroma, atherosclerosis, arterial restenosis, autoimmune diseases, acute and chronic inflammation, bone diseases and ocular diseases with retinal vessel proliferation.

INTERNATIONAL SEARCH REPORT

Internat: Application No
PCT/GB 00/03139

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/04 A61K31/437 A61P35/00 //(C07D471/04,235:00, 221:00),(C07D471/04,231:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 521 184 A (ZIMMERMANN JUERG) 28 May 1996 (1996-05-28) claims 1,21 ---	1,10
A	WO 96 40143 A (SMITHKLINE BEECHAM CORP) 19 December 1996 (1996-12-19) claims 1,22 -----	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 December 2000	08/01/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat' Application No
PCT/GB 00/03139

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2001 (15.11.2001)

PCT

(10) International Publication Number
WO 01/85700 A2

(51) International Patent Classification[7]: C07D 239/00

(21) International Application Number: PCT/EP01/04991

(22) International Filing Date: 3 May 2001 (03.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/202,472 8 May 2000 (08.05.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

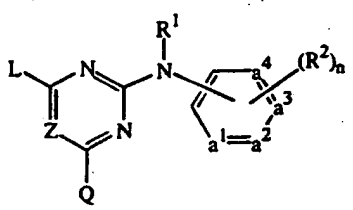
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/85700 A2

(54) Title: HIV REPLICATION INHIBITORS



(I)

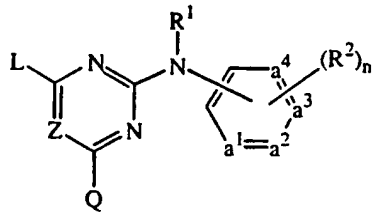
(57) Abstract: This invention concerns HIV replication inhibitors of formula (I)the N-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and the stereochemically isomeric forms thereof, provided that when Q is halo then Z is N; or when Q is polyhaloC_{1-6}alkyl then Y is hydrogen or C_{1-6}alkyl; their use as a medicine, their processes for preparation and pharmaceutical compositions comprising them.

HIV REPLICATION INHIBITORS

The present invention concerns substituted amino pyrimidine or triazine derivatives having Human Immunodeficiency Virus (HIV) replication inhibiting properties. It also relates to their use as a medicine, their processes for preparation and pharmaceutical compositions comprising them.

WO 99/50250 and WO 00/27825 disclose substituted amino pyrimidine derivatives having HIV replication inhibiting properties.
EP 0,834,507, WO 99/50256 and WO 00/27828 disclose substituted amino triazine derivatives having HIV replication inhibiting properties.
WO 95/10506 concerns N-alkyl-N-aryl-pyrimidinamines having antagonistic activity at the CRF (Corticotropin Releasing Factor) receptor. Said compounds are claimed to have a therapeutic effect on psychiatric disorders and neurological diseases.
EP 0,270,111 describes pyrimidine derivatives having fungicidal activity.
The present compounds differ from the prior art compounds by their structure and by their improved HIV replication inhibiting properties.

The present invention concerns a compound of formula (I)



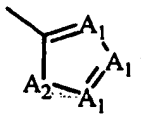
(I)

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein
$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);
-N=CH-CH=CH- (a-2);
-N=CH-N=CH- (a-3);
-N=CH-CH=N- (a-4);
-N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;
R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, -NHC(=O)H, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula



(c)

wherein each A_1 independently is N, CH or CR^6; and

A_2 is NH, O, S or NR^6;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said groups may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X^1-R^3$ or $-X^2$-Alk-R^4 wherein

Alk is C_{1-4}alkanediyl;

R^3 or R^4 each independently are phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

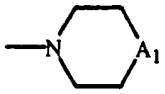
X^1 or X^2 each independently are $-NR^7-$, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, $-S(=O)_p-$;

Q represents cyano, hydroxy, mercapto, carboxyl, formyl, halo, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, mercaptoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)-aminoC_{1-6}alkyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-6}alkyl-oxy, C_{1-6}alkylthio, C_{1-6}alkyl$S(=O)_p$, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkenyl-oxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, C_{2-6}alkynyl, polyhaloC_{1-6}alkyl, hydroxy-polyhaloC_{1-6}alkyl, Het or C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy;

Z is C-Y or N wherein

Y represents hydrogen, hydroxy, halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^8$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^8$, $-NH-S(=O)_pR^8$, $-C(=O)R^8$, -NHC(=O)H, $-C(=O)NHNH_2$, $-NHC(=O)R^8$, $-C(=NH)R^8$ or aryl;

R^5 is hydrogen or a radical of formula



(d)

with A_1 being CH_2 or O;

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

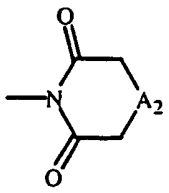
R^7 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^8 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

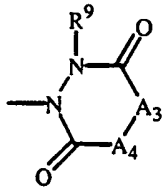
p is 1 or 2;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, tetrazolyl;

Het is imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, triazolyl, tetrazolyl optionally substituted with imino, a radical of formula (c) as described hereinabove, imidazolidinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone, or a radical of formula



(e-1)



(e-2)

with A_2 being O, CH_2 or a direct bond;

A_3 being CH_2 or NH;

A_4 being CH_2 or a direct bond; or

A_3-A_4 representing CH=CH;

R^9 being hydrogen or C_{1-4}alkylcarbonyl;

provided that when Q is halo then Z is N; or when Q is polyhaloC_{1-6}alkyl then Y is hydrogen or C_{1-6}alkyl.

As used hereinbefore or hereinafter C_{1-4}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as methyl, ethyl, propyl, 1-methylethyl, butyl and the like; C_{1-6}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as the group defined for C_{1-4}alkyl and pentyl, hexyl, 2-methylbutyl and the like; C_{1-10}alkyl as a group or part of a group defines straight or branched chain saturated hydrocarbon radicals having from 1 to 10 carbon atoms such as the groups defined for C_{1-6}alkyl and heptyl, octyl, nonyl, decyl, 2-methyl-heptyl, 3-ethyl-heptyl and the like; C_{1-4}alkanediyl defines straight or branched chain saturated bivalent hydrocarbon radicals having from 1 to 4 carbon atoms such as methylene, 1,2-ethanediyl or 1,2-ethylidene, 1,3-propanediyl or 1,3-propylidene, 1,4-butanediyl or 1,4-butylidene and the like; C_{3-7}cycloalkyl is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; C_{2-6}alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a double bond such as ethenyl, propenyl, butenyl, pentenyl, hexenyl and the like; C_{2-10}alkenyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms containing a double bond such as the groups defined for C_{2-6}alkenyl and heptenyl, octenyl, nonenyl, decenyl and the like; C_{2-6}alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 6 carbon atoms containing a triple bond such as ethynyl, propynyl, butynyl, pentynyl, hexynyl and the like; C_{2-10}alkynyl defines straight and branched chain hydrocarbon radicals having from 2 to 10 carbon atoms containing a triple bond such as the groups defined for C_{2-6}alkynyl and heptynyl, octynyl, nonynyl, decynyl and the like.

As used herein before, the term (=O) forms a carbonyl moiety when attached to a carbon atom, a sulfoxide moiety when attached to a sulfur atom and a sulfonyl moiety when two of said terms are attached to a sulfur atom.

The term halo is generic to fluoro, chloro, bromo and iodo. As used in the foregoing and hereinafter, polyhalomethyl as a group or part of a group is defined as mono- or polyhalosubstituted methyl, in particular methyl with one or more fluoro atoms, for example, difluoromethyl or trifluoromethyl; polyhaloC_{1-6}alkyl as a group or part of a group is defined as mono- or polyhalosubstituted C_{1-6}alkyl, for example, the groups defined in halomethyl, 1,1-difluoro-ethyl and the like. In case more than one halogen

atoms are attached to an alkyl group within the definition of polyhalomethyl or polyhaloC_{1-6}alkyl, they may be the same or different.

Het is meant to include all the possible isomeric forms of the heterocycles mentioned in the definition of Het, for instance, imidazolyl also includes 2*H*-imidazolyl.

The Het radical may be attached to the remainder of the molecule of formula (I) through any ring carbon or heteroatom as appropriate, if not otherwise specified. Thus, for example, when the heterocycle is imidazolyl, it may be 1-imidazolyl, 2-imidazolyl, 4-imidazolyl and the like.

When any variable (eg. aryl, R^2, etc.) occurs more than one time in any constituent, each definition is independent.

Lines drawn into ring systems from substituents indicate that the bond may be attached to any of the suitable ring atoms.

For therapeutic use, salts of the compounds of formula (I) are those wherein the counterion is pharmaceutically acceptable. However, salts of acids and bases which are non-pharmaceutically acceptable may also find use, for example, in the preparation or purification of a pharmaceutically acceptable compound. All salts, whether pharmaceutically acceptable or not are included within the ambit of the present invention.

The pharmaceutically acceptable addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The latter can conveniently be obtained by treating the base form with such appropriate acids as inorganic acids, for example, hydrohalic acids, e.g. hydrochloric, hydrobromic and the like; sulfuric acid; nitric acid; phosphoric acid and the like; or organic acids, for example, acetic, propanoic, hydroxy-acetic, 2-hydroxypropanoic, 2-oxopropanoic, oxalic, malonic, succinic, maleic, fumaric, malic, tartaric, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely the salt form can be converted by treatment with alkali into the free base form.

The compounds of formula (I) containing acidic protons may be converted into their therapeutically active non-toxic metal or amine addition salt forms by treatment with

appropriate organic and inorganic bases. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. primary, secondary and tertiary aliphatic and aromatic amines such as methylamine, ethylamine, propylamine, isopropylamine, the four butylamine isomers, dimethylamine, diethylamine, diethanolamine, dipropylamine, diisopropylamine, di-n-butylamine, pyrrolidine, piperidine, morpholine, trimethylamine, triethylamine, tripropylamine, quinuclidine, pyridine, quinoline and isoquinoline, the benzathine, *N*-methyl-D-glucamine, 2-amino-2-(hydroxymethyl)-1,3-propanediol, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like. Conversely the salt form can be converted by treatment with acid into the free acid form.
The term addition salt also comprises the hydrates and solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term "quaternary amine" as used hereinbefore defines the quaternary ammonium salts which the compounds of formula (I) are able to form by reaction between a basic nitrogen of a compound of formula (I) and an appropriate quaternizing agent, such as, for example, an optionally substituted alkylhalide, arylhalide or arylalkylhalide, e.g. methyliodide or benzyliodide. Other reactants with good leaving groups may also be used, such as alkyl trifluoromethanesulfonates, alkyl methanesulfonates, and alkyl p-toluenesulfonates. A quaternary amine has a positively charged nitrogen. Pharmaceutically acceptable counterions include chloro, bromo, iodo, trifluoroacetate and acetate. The counterion of choice can be introduced using ion exchange resins.

It will be appreciated that some of the compounds of formula (I) and their *N*-oxides, addition salts, quaternary amines and stereochemically isomeric forms may contain one or more centers of chirality and exist as stereochemically isomeric forms.

The term "stereochemically isomeric forms" as used hereinbefore defines all the possible stereoisomeric forms which the compounds of formula (I), and their *N*-oxides, addition salts, quaternary amines or physiologically functional derivatives may possess. Unless otherwise mentioned or indicated, the chemical designation of compounds denotes the mixture of all possible stereochemically isomeric forms, said mixtures containing all diastereomers and enantiomers of the basic molecular structure as well as each of the individual isomeric forms of formula (I) and their *N*-oxides, salts, solvates or quaternary amines substantially free, *i.e.* associated with less than 10%, preferably

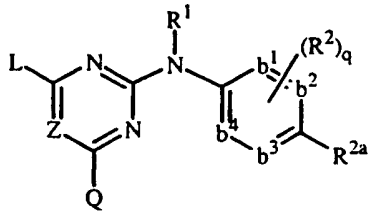
less than 5%, in particular less than 2% and most preferably less than 1% of the other isomers. In particular, stereogenic centers may have the R- or S-configuration; substituents on bivalent cyclic (partially) saturated radicals may have either the *cis*- or *trans*-configuration. Compounds encompassing double bonds can have an E or Z-stereochemistry at said double bond. Stereochemically isomeric forms of the compounds of formula (I) are obviously intended to be embraced within the scope of this invention.

The *N*-oxide forms of the present compounds are meant to comprise the compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide.

Some of the compounds of formula (I) may also exist in their tautomeric form. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to also include their *N*-oxide forms, their salts, their quaternary amines and their stereochemically isomeric forms. Of special interest are those compounds of formula (I) which are stereochemically pure.

An interesting group of compounds are those compounds of formula (I) having the formula



(I)

the *N*-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and the stereochemically isomeric forms thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

$-N=CH-C(R^{2a})=CH-N=$ (b-5);

$-CH=N-C(R^{2a})=N-CH=$ (b-6);

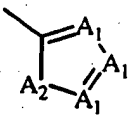
$-N=N-C(R^{2a})=CH-CH=$ (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, -NHC(=O)H, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula



(c)

wherein each A_1 independently is N, CH or CR^6; and

A_2 is NH, O, S or NR^6;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said groups may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,
* phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X^1-R^3$ or $-X^2$-Alk-R^4 wherein

Alk is C_{1-4}alkanediyl;

R^3 or R^4 each independently are phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

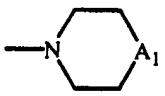
X^1 or X^2 each independently are $-NR^7-$, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, $-S(=O)_p-$;

Q represents cyano, hydroxy, mercapto, carboxyl, formyl, halo, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, mercaptoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)-aminoC_{1-6}alkyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-6}alkyl-oxy, C_{1-6}alkylthio, C_{1-6}alkylS(=O)$_p$, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkenyl-oxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, C_{2-6}alkynyl, polyhaloC_{1-6}alkyl, hydroxy-polyhaloC_{1-6}alkyl, Het or C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy;

Z is C-Y or N wherein

Y represents hydrogen, hydroxy, halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or -C(=O)R^8, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalo-methylthio, -S(=O)$_p$$R^8$, -NH-S(=O)$_p$$R^8$, -C(=O)$R^8$, -NHC(=O)H, -C(=O)NHNH$_2$, -NHC(=O)$R^8$,-C(=NH)$R^8$ or aryl;

R^5 is hydrogen or a radical of formula


(d)

with A_1 being CH_2 or O;

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

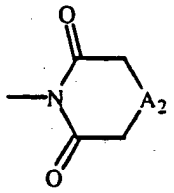
R^7 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^8 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

p is 1 or 2;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, tetrazolyl;

Het is imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, triazolyl, tetrazolyl optionally substituted with imino, a radical of formula (c) as described hereinabove, imidazolidinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone, or a radical of formula



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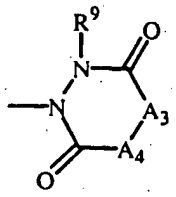


(e-2)

with A_2 being O, CH_2 or a direct bond;

A_3 being CH_2 or NH;

A_4 being CH_2 or a direct bond; or

A_3-A_4 representing CH=CH;

R^9 being hydrogen or C_{1-4}alkylcarbonyl;

provided that when Q is halo then Z is N; or when Q is polyhaloC_{1-6}alkyl then Y is hydrogen or C_{1-6}alkyl.

Another interesting group of compounds are those compounds of formula (I) or (I') wherein Q is cyano, hydroxy, mercapto, carboxyl, formyl, cyanoC_{1-6}alkyl, hydroxy-C_{1-6}alkyl, mercaptoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)amino-C_{1-6}alkyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-6}alkyloxy-C_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylS(=O)$_p$, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkenyloxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, C_{2-6}alkynyl, hydroxypolyhaloC_{1-6}alkyl, or Het.

Also an interesting group of compounds are those compounds of formula (I) or (I') wherein Q is cyano, hydroxy, mercapto, carboxyl, hydroxyC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, aminocarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylS(=O), C_{1-6}alkyloxycarbonyl, halo, polyhaloC_{1-6}alkyl, C_{2-6}alkenyloxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, a radical of formula (c) or (e-1) or (e-2), imidazolyl, triazolyl, tetrazolyl optionally substituted with imino, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone.

A further interesting group of compounds are those compounds of formula (I) or (I') wherein Q is cyano, hydroxy, mercapto, carboxyl, hydroxyC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, aminocarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylS(=O), C_{1-6}alkyloxycarbonyl, C_{2-6}alkenyloxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, a radical of formula (c) or (e-1) or (e-2), imidazolyl, triazolyl,

tetrazolyl optionally substituted with imino, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone.

Still a further interesting group of compounds are those compounds of formula (I) or (I') wherein Z is C-Y.

Still another interesting group of compounds are those compounds of formula (I) or (I') wherein Z is N.

Also an interesting group of compounds are those compounds of formula (I) or (I') wherein Z is C-Y and Q is hydroxyC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, polyhaloC_{1-6}alkyl, aminocarbonyl, imidazolyl.

Also an interesting group of compounds are those compounds of formula (I) or (I') wherein Z is C-Y and Q is hydroxyC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy, carboxyl, C_{1-6}alkyloxycarbonyl, aminocarbonyl, imidazolyl.

Yet another interesting group of compounds are those compounds of formula (I) or (I') wherein Z is N and Q is cyano, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, sulfhydryl, C_{1-6}alkylS(=O), aminocarbonyl, halo, C_{2-6}alkenyloxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, a radical of formula (c) or (e-1) or (e-2), imidazolyl, triazolyl, tetrazolyl optionally substituted with imino, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone.

Also an interesting group of compounds are those compounds of formula (I) or (I') wherein Z is N and Q is cyano, hydroxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, sulfhydryl, C_{1-6}alkylS(=O), aminocarbonyl, C_{2-6}alkenyloxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, a radical of formula (c) or (e-1) or (e-2), imidazolyl, triazolyl, tetrazolyl optionally substituted with imino, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone.

Yet another interesting group of compounds are those compounds of formula (I) or (I') wherein L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said groups may be substituted with one or two substituents independently selected from C_{3-7}cycloalkyl; indolyl or isoindolyl, each optionally substituted with one, two, three or

four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl; phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or L is $-X^1-R^3$.

Still another interesting group of compounds are those compounds of formula (I) or (I') wherein Y is hydroxy, halo, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^8$, C_{1-6}alkyloxy, C_{1-6}alkyloxy-carbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^8$, $-NH-S(=O)_pR^8$, $-C(=O)R^8$, $-NHC(=O)H$, $-C(=O)NHNH_2$, $-NHC(=O)R^8$,$-C(=NH)R^8$ or aryl.

Also an interesting group of compounds are those compounds of formula (I) wherein $-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula -CH=CH-CH=CH- (a-1) or -N=CH-CH=CH- (a-2).

Also an interesting group of compounds are those compounds of formula (I') wherein $-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula $-CH=CH-C(R^{2a})=CH-CH=$ (b-1) or $-CH=N-C(R^{2a})=CH-CH=$ (b-3).

Still another interesting group of compounds are those compounds of formula (I) or (I') wherein L is $-X-R^3$ wherein R^3 is 2,4,6-trisubstituted phenyl, wherein each substituent is independently selected from chloro, bromo, fluoro, cyano or C_{1-4}alkyl.

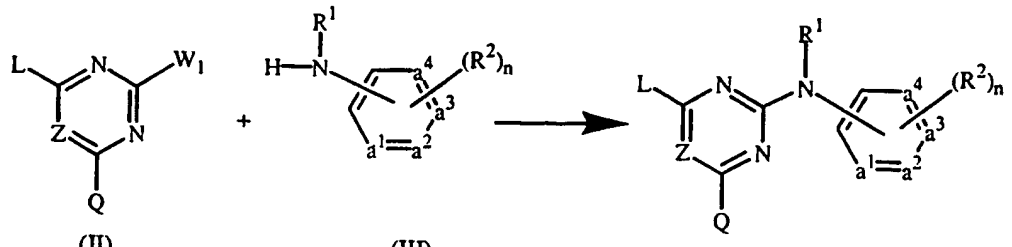
Particular compounds are those compounds of formula (I) or (I') wherein the moiety in the 2 position of the pyrimidine ring is a 4-cyano-anilino group or a 4-aminocarbonyl-anilino group.

Preferred compounds are those compounds of formula (I) or (I') wherein the moiety in the 2 position of the pyrimidine ring is a 4-cyano-anilino group, L is $-X-R^3$ wherein R^3 is a 2,4,6-trisubstituted phenyl, Z is N or C-Y with Y being halo or hydrogen and Q is hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, cyano or Het.

Preferred compounds of formula (I) or (I') are selected from

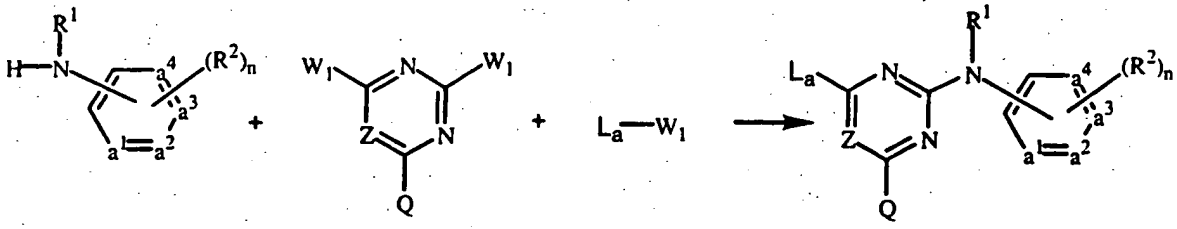
4-[[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-hydroxymethyl]-2-pyrimidinyl]amino]benzonitrile;
4-[[[6-chloro-4-(2,4,6-trimethylphenylamino)]-1,3,5-triazin-2-yl]amino]benzonitrile;
4-[[[6-trifluoromethyl-2-(4-cyanophenylamino)]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;
6-[(4-cyanophenyl)amino]-4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazine-2-carboxamide;
4-[[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-methoxymethyl]-2-pyrimidinyl]amino]benzonitrile;
4-[[[5-bromo-4-(4-cyano-2,6-dibromophenoxy)-6-hydroxymethyl]2-pyrimidinyl]amino]benzonitrile;
2-[(4-cyanophenyl)amino]-6-[(2,4,6-trimethylphenyl)amino]-4-pyrimidine carboxamide;
5-bromo-2-[(4-cyanophenyl)amino]-6-[(2,4,6-trimethylphenyl)amino]-4-pyrimidine carboxamide;
their N-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof.

In general, compounds of formula (I) can be prepared by reacting an intermediate of formula (II) wherein W_1 is a suitable leaving group such as, for example, a halogen, hydroxy, triflate, tosylate, thiomethyl, methylsulfonyl, trifluoromethylsulfonyl and the like, with an amino derivative of formula (III) under solvent-free conditions or in a suitable solvent such as, for example, water, ethanol, 1-methyl-2-pyrrolidinone, *N,N*-dimethylformamide, 1,4-dioxane, 1,2-dimethoxy-ethane, tetrahydrofuran, dimethyl sulfoxide, tetraline, sulfolane, acetonitrile, toluene and the like, optionally under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, optionally in the presence of a suitable acid such as, for example, 1 N hydrochloric acid in diethyl ether or the like or a suitable base, such as *N*, *N*-diisopropylethanamine, NaI, BuOH, and optionally in the presence of a suitable catalyst, such as for example tetrakis(triphenylphosphine) palladium. This reaction can be performed at a temperature ranging between 50°C and 250°C.



(II) (III) (I)

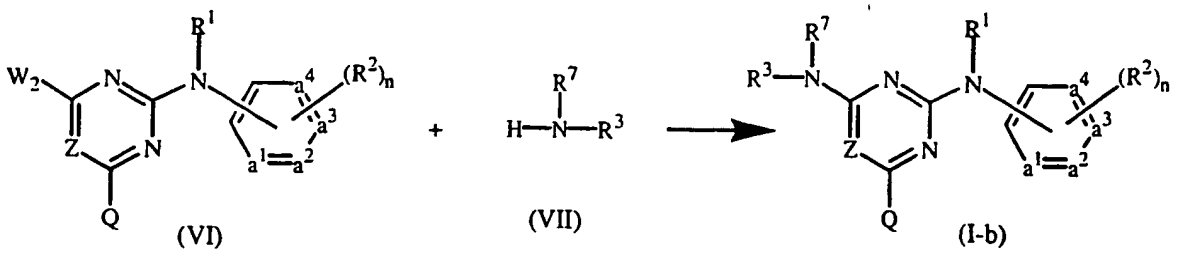
Alternatively, a compound of formula (I) wherein L represents C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said groups may be substituted with one or two substituents independently selected from C_{3-7}cycloalkyl; indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl; phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2, said L being represented by L_a, and said compounds being represented by formula (I-a), can also be prepared by reacting an intermediate of formula (III) with an intermediate of formula (IV) and an intermediate of formula (V) in the presence of magnesium and in the presence of a suitable solvent such as diethylether, benzene, 1,4-dioxane, *N,N*-diethylethanamine.



(III) (IV) (V) (I-a)

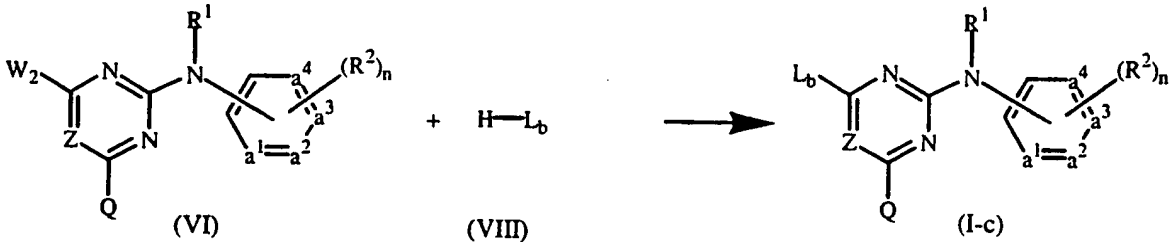
In this and the following preparations, the reaction products may be isolated from the reaction medium and, if necessary, further purified according to methodologies generally known in the art such as, for example, extraction, crystallization, distillation, trituration and chromatography.

The compounds of formula (I) wherein L is a radical of formula $-NR^7-R^3$, said compounds being represented by formula (I-b), can be prepared by reacting an intermediate of formula (VI) wherein W_2 is a suitable leaving group such as, for example, a halogen or a triflate, with an intermediate of formula (VII) under solvent-free conditions or in an appropriate solvent such as, for example, ethanol, 1-methyl-2-pyrrolidinone, *N,N*-dimethylformamide, 1,4-dioxane, tetrahydrofuran, dimethyl sulfoxide, tetraline, sulfolane, acetonitrile and the like, under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, and optionally in the presence of a suitable acid such as, for example, 1 N hydrochloric acid in diethyl ether or the like or a suitable base, such as *N, N*-diisopropylethanamine. This reaction can be performed at a temperature ranging between 50°C and 250°C.



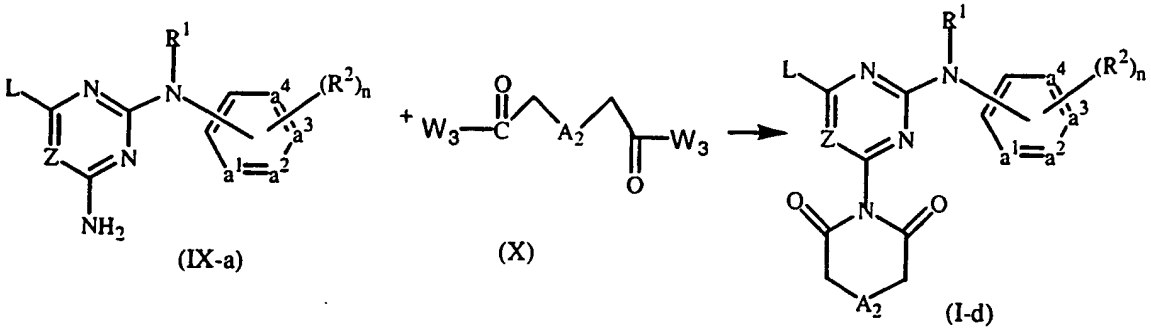
(VI) (VII) (I-b)

The compounds of formula (I) wherein L is a radical of formula $-X^1-R^3$ or $-X^2$-Alk-R^4, said L being represented by L_b, and said compounds being represented by formula (I-c), can be prepared by reacting an intermediate of formula (VI) wherein W_2 is a suitable leaving group such as, for example a halogen or a triflate, with an intermediate of formula (VIII) in an appropriate solvent such as, for example, 1-methyl-2-pyrrolidinone, 1,4-dioxane, dimethyl sulfoxide, tetraline, sulfolane, tetrahydrofuran, acetone, acetone/water and the like under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, and in the presence of a suitable base such as, for example, sodium hydride, potassium hydride, sodium hydroxide, *N*, *N*-diisopropyl-ethanamine or the like. This reaction can be performed at a temperature ranging between 50°C and 250°C.



(VI) (VIII) (I-c)

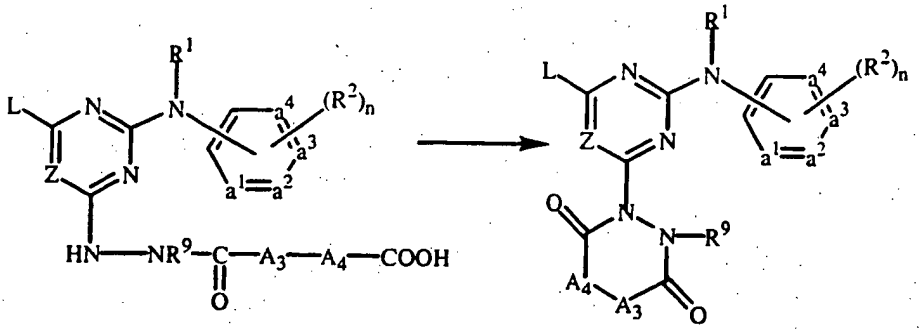
The compounds of formula (I) wherein Q is a radical of formula (e-1), said compounds being represented by formula (I-d), can be prepared by reacting an intermediate of formula (IX-a) with an intermediate of formula (X), wherein W_3 represents a suitable leaving group, such as a halogen, e.g. chloro, bromo and the like.



(IX-a) (X) (I-d)

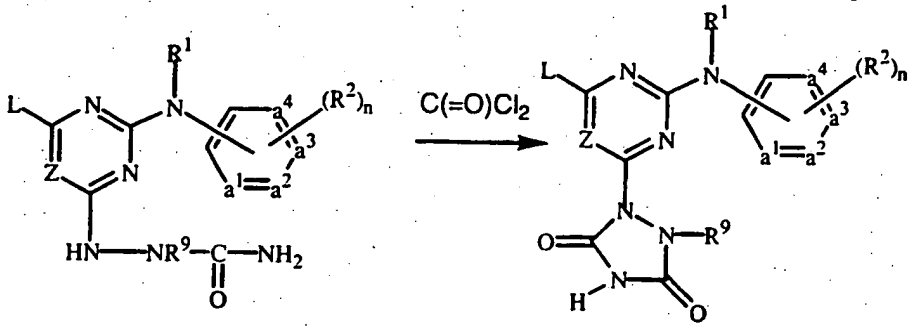
The compounds of formula (I), wherein Q is a radical of formula (e-2), said compounds being represented by formula (I-e), can be prepared by cycling an intermediate of

formula (IX-b) in the presence of a suitable carbonic derivative, such as for example acetic acid anhydride, and in the presence of a suitable base, such as sodium acetate.



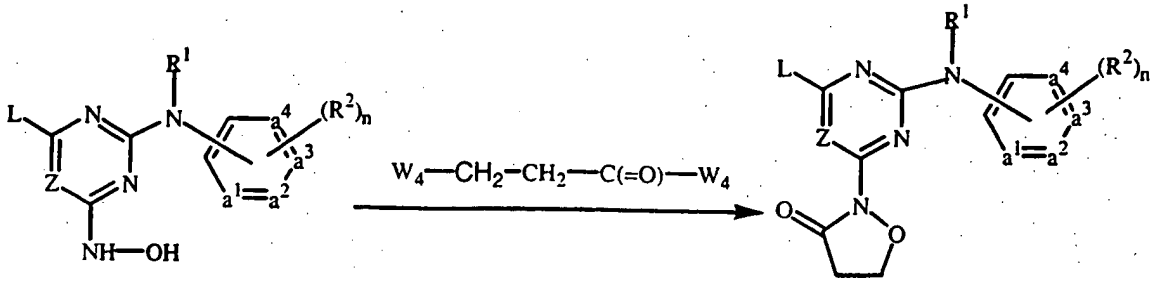
(IX-b) (I-e)

The compounds of formula (I-e), wherein A_3 is NH and A_4 is a direct bond, said compounds being represented by formula (I-e-1), can be prepared by reacting an intermediate of formula (IX-c) with a carbonic derivative, such as for example carbonic dichloride, in the presence of a suitable solvent, such as for example dioxane.



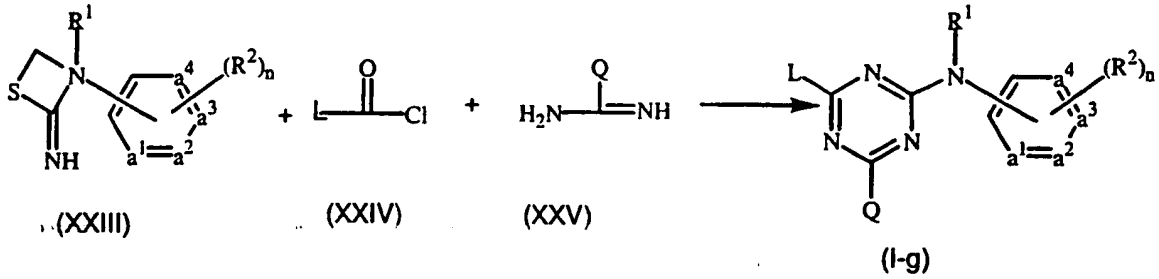
(IX-c) (I-e-1)

The compounds of formula (I), wherein Q is isoxazolidinone, said compounds being represented by formula (I-f), can be prepared by reacting an intermediate of formula (IX-d) with W_4-CH_2-CH_2-C(=O)-W_4, wherein W_4 represents a suitable leaving group, such as a halogen, e.g. chloro, bromo and the like, in the presence of a suitable base, such as for example *N N* -diethylethanamine, and a suitable solvent, such as tetrahydrofuran.



(IX-d) (I-f)

The compounds of formula (I) wherein Z is N, said compounds being represented by formula (I-g), can be prepared by reacting an intermediate of formula (XXIII) with an intermediate of formula (XXIV) and an intermediate of formula (XXV) in the presence of a suitable base, such as for example sodium acetate or Na_2CO_3, and a suitable solvent, such as acetonitrile.



(XXIII) (XXIV) (XXV) (I-g)

The compounds of formula (I) may further be prepared by converting compounds of formula (I) into each other according to art-known group transformation reactions.

The compounds of formula (I) may be converted to the corresponding *N*-oxide forms following art-known procedures for converting a trivalent nitrogen into its *N*-oxide form. Said *N*-oxidation reaction may generally be carried out by reacting the starting material of formula (I) with an appropriate organic or inorganic peroxide. Appropriate inorganic peroxides comprise, for example, hydrogen peroxide, alkali metal or earth alkaline metal peroxides, e.g. sodium peroxide, potassium peroxide; appropriate organic peroxides may comprise peroxy acids such as, for example, benzenecarboperoxoic acid or halo substituted benzenecarboperoxoic acid, e.g. 3-chlorobenzenecarboperoxoic acid, peroxoalkanoic acids, e.g. peroxoacetic acid, alkylhydroperoxides, e.g. tert.butyl hydro-peroxide. Suitable solvents are, for example, water, lower alcohols, e.g. ethanol and the like, hydrocarbons, e.g. toluene, ketones, e.g. 2-butanone, halogenated hydrocarbons, e.g. dichloromethane, and mixtures of such solvents.

For instance, compounds of formula (I) wherein Q is halo, can be converted into a compound of formula (I) wherein Q is cyano, by reaction with a suitable cyano-introducing agent, such as sodium cyanide or copper(I) cyanide, optionally in the presence of a suitable catalyst, such as for example tetrakis(triphenylphosphine) palladium and in the presence of a suitable solvent, such as *N*,*N*-dimethyl-aniline or 1-methyl-2-pyrrolidinone. A compound of formula (I) wherein Q is cyano, can further be converted into a compound of formula (I) wherein Q is aminocarbonyl, by reaction with HCOOH, in the presence of a suitable acid, such as hydrochloric acid. A compound of formula (I) wherein Q and R^2 are both cyano, can be converted into a

compound of formula (I) wherein Q and R^2 are both aminocarbonyl by reaction with HCOOH, in the presence of a suitable acid, such as hydrochloric acid. A compound of formula (I) wherein Q is cyano, can also further be converted into a compound of formula (I) wherein Q is tetrazolyl, by reaction with sodium azide in the presence of ammonium chloride and *N*, *N* -dimethylacetoacetamide.

Compounds of formula (I) wherein Q is halo can also be converted into a compound of formula (I) wherein Q is mercapto, by reaction with disodium sulfide in the presence of a suitable solvent, such as, for example, 1,4-dioxane.

Compounds of formula (I) wherein Q is halo can also be converted into a compound of formula (I) wherein Q is C_{1-6}alkylthio, by reaction with a suitable reagent such as alkaline metal-S-C_{1-6}alkyl, e.g. sodium-S-C_{1-6}alkyl, in the presence of a suitable solvent, such as *N*, *N* -dimethyl sulfoxide. The latter compounds of formula (I) can further be converted into a compound of formula (I) wherein Q is C_{1-6}alkyl-S(=O)-, by reaction with a suitable oxidizing agent, such as a peroxide, e.g. 3-chlorobenzenecarboperoxoic acid, in the presence of a suitable solvent, such as an alcohol, e.g. ethanol.

Compounds of formula (I) wherein Q is halo can also be converted into a compound of formula (I) wherein Q is C_{1-6}alkyloxy, by reaction with, for example, LiOC_{1-6}alkyl, in the presence of a suitable solvent, such as an alcohol, e.g. methanol.

Compounds of formula (I) wherein Q is halo can also be converted into a compound of formula (I) wherein Q is hydroxy, by reaction with a suitable carboxylate ester, e.g. sodium acetate, in a suitable reaction-inert solvent, such as, for example, *N*,*N*-dimethyl sulfoxide, followed by treating the obtained reaction product with a suitable base, such as pyridine, and acetyl chloride.

Compounds of formula (I) wherein Q is halo can also be converted into a compound of formula (I) wherein Q represents imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, triazolyl, tetrazolyl optionally substituted with imino, a radical of formula (c), imidazolidinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone, said Q being represented by -Q_b, by reaction with H-Q_b in the presence of a suitable base, such as, for example sodium hydroxide, potassium carbonate, sodium hydride, in the presence of a suitable solvent, such as, for example, 1,4-dioxane, *N*,*N*-dimethylacetamide, *N*,*N*-dimethylformamide

Compounds of formula (I) wherein Q is chloro, can be converted into a compound of formula (I) wherein Q is fluoro, by reaction with a suitable fluoride salt, such as for example potassium fluoride, in the presence of a suitable solvent, e.g. sulfolane.

Compounds of formula (I) wherein Q represents C_{1-6}alkyloxyC_{1-6}alkyl, can be converted into a compound of formula (I) wherein Q represents hydroxyC_{1-6}alkyl, by reducing the ether in the presence of a suitable agent, such as, for example, tribromoborane, and a suitable solvent, such as methylene chloride. Compounds of formula (I) wherein Q represents hydroxyC_{1-6}alkyl can be converted into a compound of formula (I) wherein Q represents haloC_{1-6}alkyl by reaction with a suitable halo-introducing agent, such as for example $SOCl_2$, in the presence of a suitable solvent, such as tetrahydrofuran and a suitable base, such as for example *N,N* - diethylethanamine. Compounds of formula (I) wherein Q represents haloC_{1-6}alkyl can be converted into a compound of formula (I) wherein Q represents mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, by reaction with a suitable amine, such as a mono- or di(C_{1-4}alkyl)amine.

Compounds of formula (I) wherein Q represents C_{1-6}alkyloxycarbonyl, can be converted into a compound of formula (I) wherein Q represents aminocarbonyl or mono- or di(C_{1-4}alkyl)aminocarbonyl by reaction with a suitable agent such as ammonia, $NH_2(C_{1-4}alkyl)$, $AlCH_3[N(C_{1-4}alkyl)_2]Cl$ optionally in the presence of a suitable acid, such as for example hydrochloric acid, and in the presence of a suitable solvent such as an alcohol, e.g. methanol, tetrahydrofuran, *N,.N*-diisopropylethanamine, an alcohol, e.g. methanol.
Compounds of formula (I) wherein Q represents C_{1-6}alkyloxycarbonyl, can also be converted into a compound of formula (I) wherein Q represents carboxyl by reaction with a suitable base, such as for example LiOH and the like, in the presence of a suitable solvent, such as for example an alcohol, e.g. methanol, and water.

Compounds of formula (I) wherein Q represents carboxyl can be converted into a compound of formula (I) wherein Q represents aminocarbonyl or mono-or di(C1-4alkyl)aminocarbonyl, by reaction with a suitable agent such as ammonia, ammonium chloride, $NH_2(C_{1-4}alkyl)$, $AlCH_3[N(C_{1-4}alkyl)_2]Cl$ in the presence of $SOCl_2$ and a suitable solvent, such as for example *N, N*-dimethylformamide and water.

Compounds of formula (I) wherein Q is a radical of formula (e-2), wherein R^9 is C_{1-4}alkylcarbonyl, can be converted into a compound of formula (I) wherein Q is a radical of formula (e-2), wherein R^9 is hydrogen, in the presence of a suitable solvent, such as an alcohol, e.g. methanol.

Compounds of formula (I) wherein Y is hydrogen can be converted into a compound wherein Y is halo, by reaction with a suitable halogenating agent, such as, for example Br_2 or 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis[tetrafluoroborate], in the presence of a suitable solvent, such as tetrahydrofuran, water, acetontrile, chloroform and optionally in the presence of a suitable base such as *N,N*-diethylethanamine or a suitable acid, such as for example acetic acid. The same type of reaction can be used to introduce a halo atom as R^2.

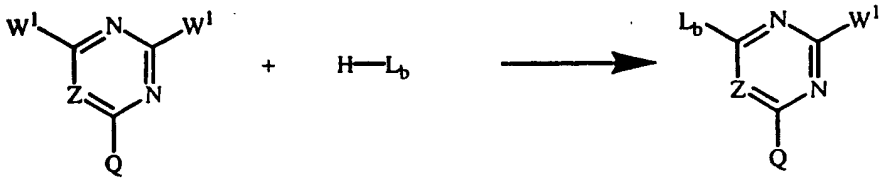
Some of the compounds of formula (I) and some of the intermediates in the present invention may contain an asymmetric carbon atom. Pure stereochemically isomeric forms of said compounds and said intermediates can be obtained by the application of art-known procedures. For example, diastereoisomers can be separated by physical methods such as selective crystallization or chromatographic techniques, e.g. counter current distribution, liquid chromatography and the like methods. Enantiomers can be obtained from racemic mixtures by first converting said racemic mixtures with suitable resolving agents such as, for example, chiral acids, to mixtures of diastereomeric salts or compounds; then physically separating said mixtures of diastereomeric salts or compounds by, for example, selective crystallization or chromatographic techniques, e.g. liquid chromatography and the like methods; and finally converting said separated diastereomeric salts or compounds into the corresponding enantiomers. Pure stereochemically isomeric forms may also be obtained from the pure stereochemically isomeric forms of the appropriate intermediates and starting materials, provided that the intervening reactions occur stereospecifically.

An alternative manner of separating the enantiomeric forms of the compounds of formula (I) and intermediates involves liquid chromatography, in particular liquid chromatography using a chiral stationary phase.

Some of the intermediates and starting materials are known compounds and may be commercially available or may be prepared according to art-known procedures or some of the compounds of formula (I) or the described intermediates may be prepared

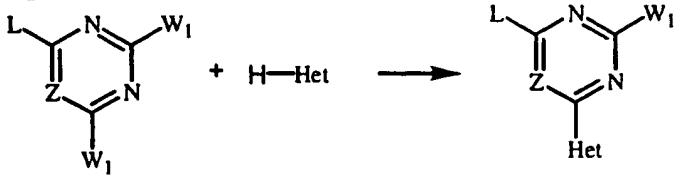
according to the procedures described in EP-0834507, WO99/50250, WO99/50256, WO 00/27825 and WO 00/27828.

Intermediates of formula (II) wherein L is $-X^1-R^3$ or $-X^2$-Alk-R^4, said L being represented by $-L_b$, and said intermediates being represented by formula (II-a), can be prepared by reacting an intermediate of formula (IV) wherein each W^1 is as defined previously, with an intermediate of formula (VIII) in the presence of a suitable solvent such as, for example, 1,4-dioxane, 2-propanol, acetone or the like, and in the presence of a suitable base such as, for example, *N,N*-diethylethanamine or *N,N*-diisopropyl-ethanamine, K_2CO_3, NaI or the like.



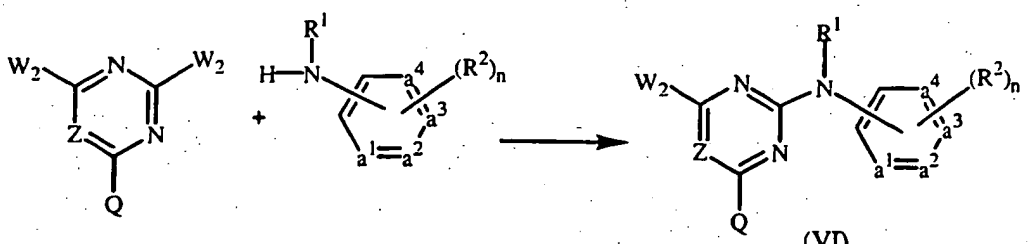
(IV) (VIII) (II-a)

Intermediates of formula (II) wherein Q is Het, said intermediates being represented by formula (II-b), can be prepared by reacting an intermediate of formula (II-c) wherein W_1 is as previously defined, with H-Het in the presence of a suitable solvent, such as for example *N,N* -dimethylacetamide and a suitable base, such as for example dipotassium carbonate.



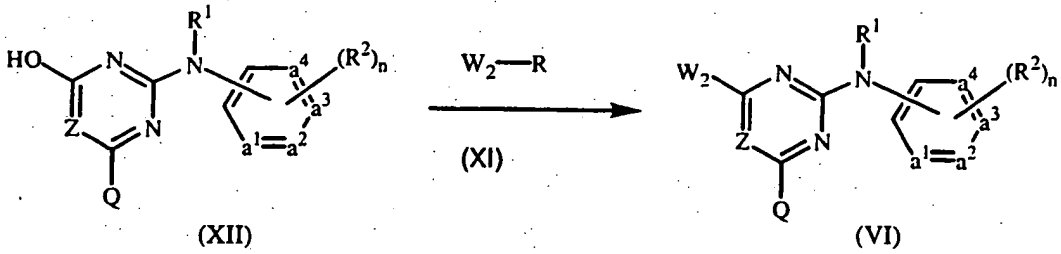
(II-c) (II-b)

Intermediates of formula (VI) can be prepared by reacting an intermediate of formula (IV-a) wherein W_2 is a suitable leaving group such as, for example, a halogen, with an intermediate of formula (III) in the presence of a suitable solvent such as, for example, 1-methyl-2-pyrrolidinone, 1,4-dioxane, tetrahydrofuran or the like, in the presence of a suitable acid such as, for example, 1 N hydrochloric acid in diethyl ether or a suitable base, such as for example *N,N* -diethylethanamine. This reaction can be performed at a temperature ranging between 50°C and 250°C.



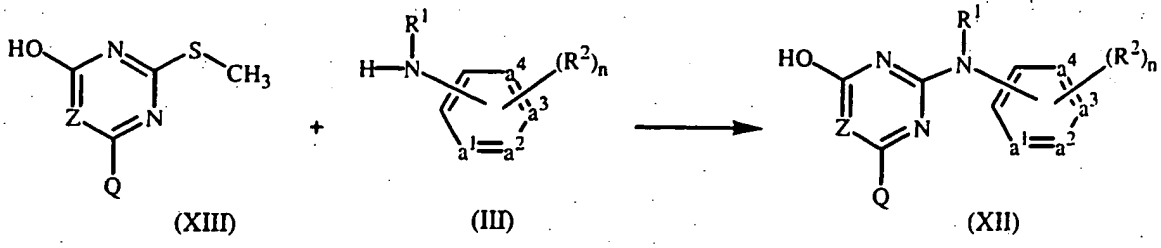
(IV-a) (III) (VI)

Alternatively, intermediates of formula (VI) can be prepared by reacting an intermediate of formula (XII) with a leaving group introducing agent of formula (XI), wherein W_2 represents the leaving group and R represents the remaining of the leaving group introducing agent, an example of a suitable leaving group introducing agent of formula (XI) is phosphorous oxychloride. The reaction can be performed under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen and at a temperature ranging between 20°C and 150°C.



(XII) (XI) (VI)

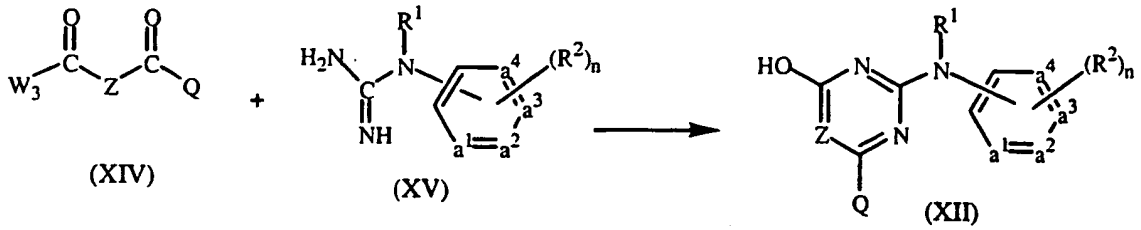
Intermediates of formula (XII) can be prepared by reacting an intermediate of formula (XIII) or a functional derivative thereof, with an intermediate of formula (III). This reaction may be performed under solvent-free conditions or in an appropriate solvent such as, for example, diglyme, tetraline or the like under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen, and optionally in the presence of a base such as, for example, sodium hydride, potassium hydride or the like. This reaction can be performed at a temperature ranging between 100°C and 250°C.



(XIII) (III) (XII)

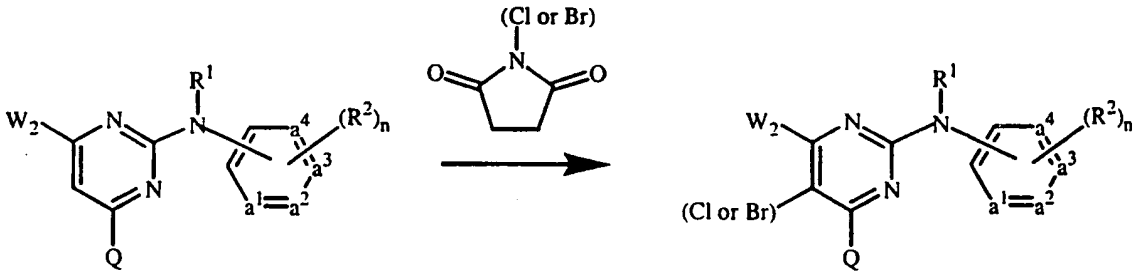
Intermediates of formula (XII) can also be prepared by reacting an intermediate of formula (XIV) wherein W_3 is a suitable leaving group, such as for example C_{1-6}alkyloxy, and Z and Q are as defined for a compound of formula (I), with an intermediate of formula (XV) in an appropriate solvent such as an alcohol, for example ethanol, or the like, and in the presence of a suitable base such as, for example, sodium

ethoxide or the like, under a reaction-inert atmosphere such as, for example, oxygen free argon or nitrogen. The reaction can be performed at a temperature ranging between 20°C and 125°C.



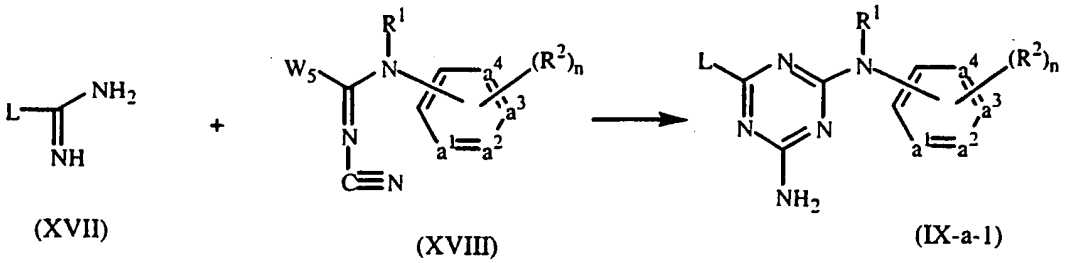
(XIV) (XV) (XII)

A convenient way of preparing an intermediate of formula (VI) wherein Z is C-Y and Y is a bromine or chloro atom, said intermediates being represented by formula (VI-a), involves the introduction of a bromine or chloro atom to an intermediate of formula (XVI), wherein W_2 is as previously defined, using *N*-bromosuccinimide or *N*-chlorosuccinimide in a reaction-inert solvent such as, for example, chloroform, carbon tetrachloride or the like. This reaction can be performed at a temperature ranging between 20°C and 125°C.



(XVI) (VI-a)

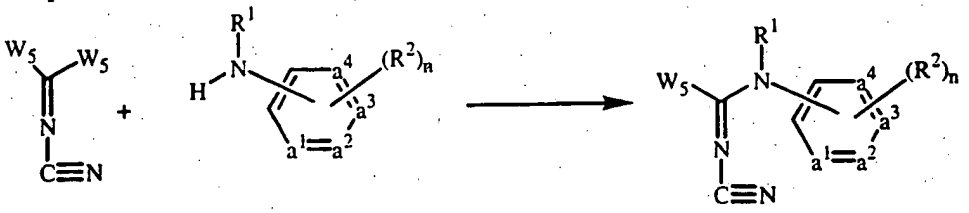
Intermediates of formula (IX-a) wherein Z is N, said intermediates being represented by formula (IX-a-1), can be prepared by reacting an intermediate of formula (XVII) with an intermediate of formula (XVIII) wherein W_5 is a suitable leaving group, such as for example phenoxy, in a suitable solvent, such as for example *N*, *N*-dimethylformamide.



(XVII) (XVIII) (IX-a-1)

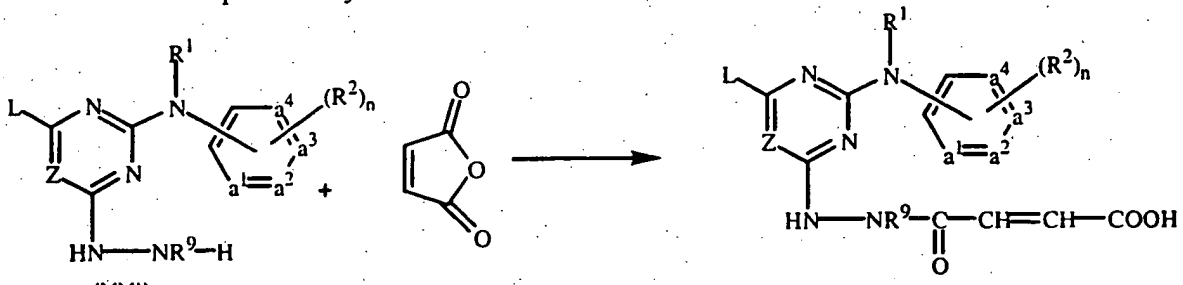
Intermediates of formula (XVIII) can be prepared by reacting an intermediate of formula (XIX) with an intermediate of formula (XX) in the presence of a suitable solvent, such as for example *N*, *N*-dimethylformamide, under a reaction-inert

atmosphere such as, for example, oxygen free argon or nitrogen, preferably at elevated temperatures.



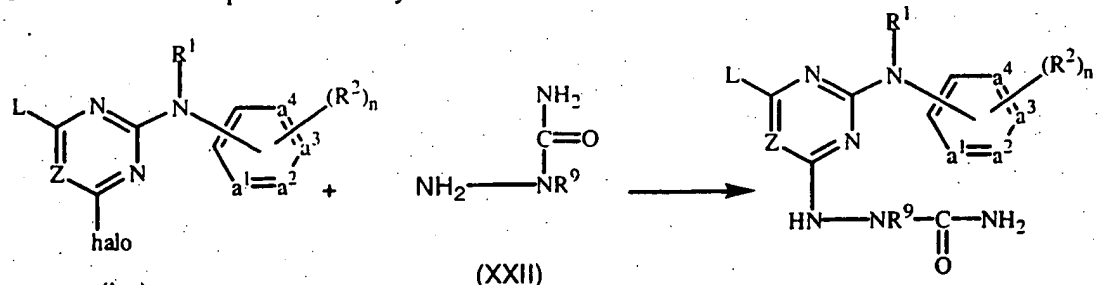
(XIX) (XX) (XVIII)

Intermediates of formula (IX-b) wherein $-A_3-A_4-$ represents $-CH=CH-$, said intermediates being represented by formula (IX-b-1), can be prepared by reacting an intermediate of formula (XXI) with 2,5-furandione in the presence of a suitable solvent, such as for example tetrahydrofuran.



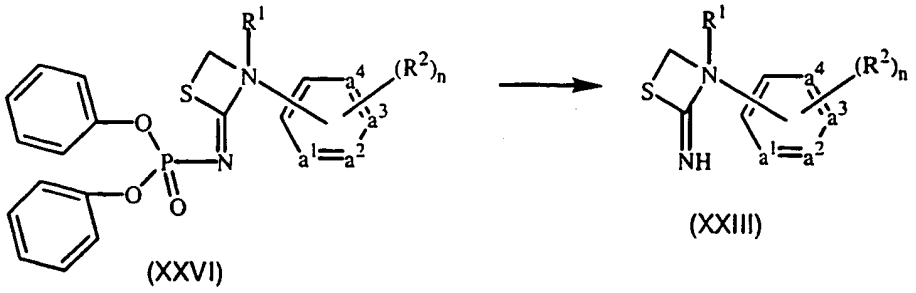
(XXI) (IX-b-1)

Intermediates of formula (IX-c) can be prepared by reacting a compound of formula (I-g) with an intermediate of formula (XXII) in the presence of a suitable solvent, such as for example pyridine or an alkanol, e.g. ethanol and the like, and a suitable base, such as for example sodium hydroxide.



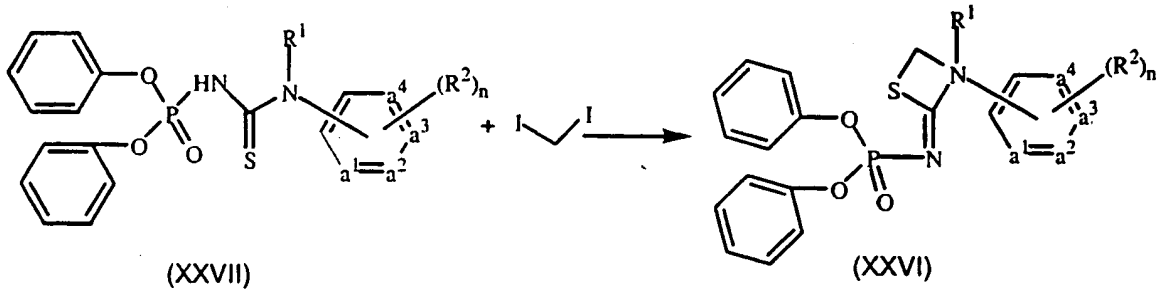
(I-g) (XXII) (IX-c)

Intermediates of formula (XXIII) can be prepared by hydrolyzing an intermediate of formula (XXVI) in the presence of a suitable acid, such as hydrochloric acid and the like, and a suitable solvent, such as for example dioxane.



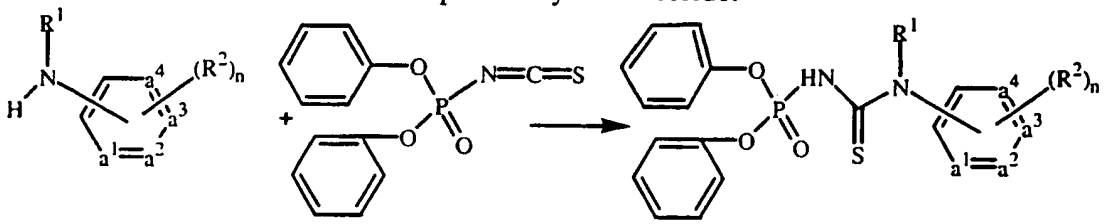
(XXVI) (XXIII)

Intermediates of formula (XXVI) can be prepared by cyclizing an intermediate of formula (XXVII) in the presence of diiodo-methane and in the presence of a suitable base such as K_2CO_3 and a suitable solvent, such as for example 2-propanone.



(XXVII) (XXVI)

Intermediates of formula (XXVII) can be prepared by reacting an intermediate of formula (III) with phosphor(isothiocyanatidic) acid, diphenyl ester in the presence of a suitable solvent, such as for example methylene chloride.



(III) (XXVII)

The compounds of formula (I) as prepared in the hereinabove described processes may be synthesized as a mixture of stereoisomeric forms, in particular in the form of racemic mixtures of enantiomers which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated therefrom by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said

compound will be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

It will be appreciated by those skilled in the art that in the processes described above the functional groups of intermediate compounds may need to be blocked by protecting groups.

Functional groups which it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl groups (e.g. *tert*-butyldimethylsilyl, *tert*-butyldiphenylsilyl or trimethylsilyl), benzyl and tetrahydropyranyl. Suitable protecting groups for amino include *tert*-butyloxycarbonyl or benzyloxycarbonyl. Suitable protecting groups for carboxylic acid include C_{1-6}alkyl or benzyl esters.

The protection and deprotection of functional groups may take place before or after a reaction step.

The use of protecting groups is fully described in 'Protective Groups in Organic Chemistry', edited by J W F McOmie, Plenum Press (1973), and 'Protective Groups in Organic Synthesis' 2nd edition, T W Greene & P G M Wutz, Wiley Interscience (1991).

The compounds of formula (I) and (I') show antiretroviral properties (reverse transcriptase inhibiting properties), in particular against Human Immunodeficiency Virus (HIV), which is the aetiological agent of Acquired Immune Deficiency Syndrome (AIDS) in humans. The HIV virus preferentially infects human T-4 cells and destroys them or changes their normal function, particularly the coordination of the immune system. As a result, an infected patient has an everdecreasing number of T-4 cells, which moreover behave abnormally. Hence, the immunological defense system is unable to combat infections and neoplasms and the HIV infected subject usually dies by opportunistic infections such as pneumonia, or by cancers. Other conditions associated with HIV infection include thrombocytopaenia, Kaposi's sarcoma and infection of the central nervous system characterized by progressive demyelination, resulting in dementia and symptoms such as, progressive dysarthria, ataxia and disorientation. HIV infection further has also been associated with peripheral neuropathy, progressive generalized lymphadenopathy (PGL) and AIDS-related complex (ARC).

The present compounds also show activity against multi drug resistant HIV strains, in particular multi drug resistant HIV-1 strains, more in particular the present compounds

show activity against HIV strains, especially HIV-1 strains, that have acquired resistance to art-known non-nucleoside reverse transcriptase inhibitors. Art-known non-nucleoside reverse transcriptase inhibitors are those non-nucleoside reverse transcriptase inhibitors other than the present compounds. The present compounds also have little or no binding affinity to human α-1 acid glycoprotein.

Due to their antiretroviral properties, particularly their anti-HIV properties, especially their anti-HIV-1-activity, the compounds of formula (I) or (I'), their *N*-oxides, pharmaceutically acceptable addition salts, quaternary amines and stereochemically isomeric forms thereof, are useful in the treatment of individuals infected by HIV and for the prophylaxis of these infections. In general, the compounds of the present invention may be useful in the treatment of warm-blooded animals infected with viruses whose existence is mediated by, or depends upon, the enzyme reverse transcriptase. Conditions which may be prevented or treated with the compounds of the present invention, especially conditions associated with HIV and other pathogenic retroviruses, include AIDS, AIDS-related complex (ARC), progressive generalized lymphadenopathy (PGL), as well as chronic CNS diseases caused by retroviruses, such as, for example HIV mediated dementia and multiple sclerosis.

The compounds of the present invention or any subgroup thereof may therefore be used as medicines against above-mentioned conditions. Said use as a medicine or method of treatment comprises the systemic administration to HIV-infected subjects of an amount effective to combat the conditions associated with HIV and other pathogenic retroviruses, especially HIV-1. In particular, the compounds of formula (I) or (I') may be used in the manufacture of a medicament for the treatment or the prevention of HIV infections.

In view of the utility of the compounds of formula (I) or (I'), there is provided a method of treating warm-blooded animals, including humans, suffering from or a method of preventing warm-blooded animals, including humans, to suffer from viral infections, especially HIV infections. Said method comprises the administration, preferably oral administration, of an effective amount of a compound of formula (I) or (I'), a *N*-oxide form, a pharmaceutically acceptable addition salt, a quaternary amine or a possible stereoisomeric form thereof, to warm-blooded animals, including humans.

The present invention also provides compositions for treating viral infections comprising a therapeutically effective amount of a compound of formula (I) or (I') and a pharmaceutically acceptable carrier or diluent.

The compounds of the present invention or any subgroup thereof may be formulated into various pharmaceutical forms for administration purposes. As appropriate compositions there may be cited all compositions usually employed for systemically administering drugs. To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, optionally in addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, particularly, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs, emulsions and solutions; or solid carriers such as starches, sugars, kaolin, diluents, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules, and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit forms, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not introduce a significant deleterious effect on the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment. The compounds of the present invention may also be administered via inhalation or insufflation by means of methods and formulations employed in the art for administration via this way. Thus, in general the compounds of the present invention may be administered to the lungs in the form of a solution, a suspension or a dry powder. Any system developed for the delivery of solutions, suspensions or dry

powders via oral or nasal inhalation or insufflation are suitable for the administration of the present compounds.

To aid solubility of the compounds of formula (I) or (I'), suitable ingredients, e.g. cyclodextrins, may be included in the compositions. Appropriate cyclodextrins are α-, β-, γ-cyclodextrins or ethers and mixed ethers thereof wherein one or more of the hydroxy groups of the anhydroglucose units of the cyclodextrin are substituted with C_{1-6}alkyl, particularly methyl, ethyl or isopropyl, e.g. randomly methylated β-CD; hydroxyC_{1-6}alkyl, particularly hydroxyethyl, hydroxy-propyl or hydroxybutyl; carboxyC_{1-6}alkyl, particularly carboxymethyl or carboxy-ethyl; C_{1-6}alkylcarbonyl, particularly acetyl. Especially noteworthy as complexants and/or solubilizers are β-CD, randomly methylated β-CD, 2,6-dimethyl-β-CD, 2-hydroxyethyl-β-CD, 2-hydroxy-ethyl-γ-CD, 2-hydroxypropyl-γ-CD and (2-carboxymethoxy)propyl-β-CD, and in particular 2-hydroxypropyl-β-CD (2-HP-β-CD).

The term mixed ether denotes cyclodextrin derivatives wherein at least two cyclodextrin hydroxy groups are etherified with different groups such as, for example, hydroxy-propyl and hydroxyethyl.

The average molar substitution (M.*S*.) is used as a measure of the average number of moles of alkoxy units per mole of anhydroglucose. The average substitution degree (D.*S*.) refers to the average number of substituted hydroxyls per anhydroglucose unit. The M.*S*. and D.*S*. value can be determined by various analytical techniques such as nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR). Depending on the technique used, slightly different values may be obtained for one given cyclodextrin derivative. Preferably, as measured by mass spectrometry, the M.*S*. ranges from 0.125 to 10 and the D.*S*. ranges from 0.125 to 3.

Other suitable compositions for oral or rectal administration comprise particles consisting of a solid dispersion comprising a compound of formula (I) or (I') and one or more appropriate pharmaceutically acceptable water-soluble polymers.

The term "a solid dispersion" used hereinafter defines a system in a solid state (as opposed to a liquid or gaseous state) comprising at least two components, in casu the compound of formula (I) or (I') and the water-soluble polymer, wherein one component is dispersed more or less evenly throughout the other component or components (in case additional pharmaceutically acceptable formulating agents, generally known in the art, are included, such as plasticizers, preservatives and the like). When said dispersion

of the components is such that the system is chemically and physically uniform or homogenous throughout or consists of one phase as defined in thermo-dynamics, such a solid dispersion will be called "a solid solution". Solid solutions are preferred physical systems because the components therein are usually readily bioavailable to the organisms to which they are administered. This advantage can probably be explained by the ease with which said solid solutions can form liquid solutions when contacted with a liquid medium such as the gastro-intestinal juices. The ease of dissolution may be attributed at least in part to the fact that the energy required for dissolution of the components from a solid solution is less than that required for the dissolution of components from a crystalline or microcrystalline solid phase.

The term "a solid dispersion" also comprises dispersions which are less homogenous throughout than solid solutions. Such dispersions are not chemically and physically uniform throughout or comprise more than one phase. For example, the term "a solid dispersion" also relates to a system having domains or small regions wherein amorphous, microcrystalline or crystalline compound of formula (I) or (I'), or amorphous, microcrystalline or crystalline water-soluble polymer, or both, are dispersed more or less evenly in another phase comprising water-soluble polymer, or compound of formula (I) or (I'), or a solid solution comprising compound of formula (I) or (I') and water-soluble polymer. Said domains are regions within the solid dispersion distinctively marked by some physical feature, small in size, and evenly and randomly distributed throughout the solid dispersion.

Various techniques exist for preparing solid dispersions including melt-extrusion, spray-drying and solution-evaporation.

The solution-evaporation process comprises the following steps :

a) dissolving the compound of formula (I) or (I') and the water-soluble polymer in an appropriate solvent, optionally at elevated temperatures;

b) heating the solution resulting under point a), optionally under vacuum, until the solvent is evaporated. The solution may also be poured onto a large surface so as to form a thin film, and evaporating the solvent therefrom.

In the spray-drying technique, the two components are also dissolved in an appropriate solvent and the resulting solution is then sprayed through the nozzle of a spray dryer followed by evaporating the solvent from the resulting droplets at elevated temperatures.

The preferred technique for preparing solid dispersions is the melt-extrusion process comprising the following steps :

a) mixing a compound of formula (I) or (I') and an appropriate water-soluble polymer,
b) optionally blending additives with the thus obtained mixture,
c) heating and compounding the thus obtained blend until one obtains a homogenous melt,
d) forcing the thus obtained melt through one or more nozzles; and
e) cooling the melt till it solidifies.

The terms "melt" and "melting" should be interpreted broadly. These terms not only mean the alteration from a solid state to a liquid state, but can also refer to a transition to a glassy state or a rubbery state, and in which it is possible for one component of the mixture to get embedded more or less homogeneously into the other. In particular cases, one component will melt and the other component(s) will dissolve in the melt thus forming a solution, which upon cooling may form a solid solution having advantageous dissolution properties.

After preparing the solid dispersions as described hereinabove, the obtained products can be optionally milled and sieved.

The solid dispersion product may be milled or ground to particles having a particle size of less than 600 μm, preferably less than 400 μm and most preferably less than 125 μm.

The particles prepared as described hereinabove can then be formulated by conventional techniques into pharmaceutical dosage forms such as tablets and capsules.

It will be appreciated that a person of skill in the art will be able to optimize the parameters of the solid dispersion preparation techniques described above, such as the most appropriate solvent, the working temperature, the kind of apparatus being used, the rate of spray-drying, the throughput rate in the melt-extruder

The water-soluble polymers in the particles are polymers that have an apparent viscosity, when dissolved at 20°C in an aqueous solution at 2 % (w/v), of 1 to 5000 mPa.s more preferably of 1 to 700 mPa.s, and most preferred of 1 to 100 mPa.s. For example, suitable water-soluble polymers include alkylcelluloses, hydroxyalkylcelluloses, hydroxyalkyl alkylcelluloses, carboxyalkylcelluloses, alkali metal salts of carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters,

starches, pectines, chitin derivates, di-, oligo- and polysaccharides such as trehalose, alginic acid or alkali metal and ammonium salts thereof, carrageenans, galactomannans, tragacanth, agar-agar, gummi arabicum, guar gummi and xanthan gummi, polyacrylic acids and the salts thereof, polymethacrylic acids and the salts thereof, methacrylate copolymers, polyvinylalcohol, polyvinylpyrrolidone, copolymers of polyvinyl-pyrrolidone with vinyl acetate, combinations of polyvinylalcohol and polyvinyl-pyrrolidone, polyalkylene oxides and copolymers of ethylene oxide and propylene oxide. Preferred water-soluble polymers are hydroxypropyl methylcelluloses.

Also one or more cyclodextrins can be used as water soluble polymer in the preparation of the above-mentioned particles as is disclosed in WO 97/18839. Said cyclodextrins include the pharmaceutically acceptable unsubstituted and substituted cyclodextrins known in the art, more particularly α, β or γ cyclodextrins or the pharmaceutically acceptable derivatives thereof.

Substituted cyclodextrins which can be used to prepare the above described particles include polyethers described in U.S. Patent 3,459,731. Further substituted cyclo-dextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-6}alkyl, hydroxyC_{1-6}alkyl, carboxy-C_{1-6}alkyl or C_{1-6}alkyloxycarbonyl-C_{1-6}alkyl or mixed ethers thereof. In particular such substituted cyclodextrins are ethers wherein the hydrogen of one or more cyclodextrin hydroxy groups is replaced by C_{1-3}alkyl, hydroxyC_{2-4}alkyl or carboxyC_{1-2}alkyl or more in particular by methyl, ethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, carboxy-methyl or carboxyethyl.

Of particular utility are the β-cyclodextrin ethers, e.g. dimethyl-β-cyclodextrin as described in Drugs of the Future, Vol. 9, No. 8, p. 577-578 by M. Nogradi (1984) and polyethers, e.g. hydroxypropyl β-cyclodextrin and hydroxyethyl β-cyclodextrin, being examples. Such an alkyl ether may be a methyl ether with a degree of substitution of about 0.125 to 3, e.g. about 0.3 to 2. Such a hydroxypropyl cyclodextrin may for example be formed from the reaction between β-cyclodextrin an propylene oxide and may have a MS value of about 0.125 to 10, e.g. about 0.3 to 3.

Another type of substituted cyclodextrins is sulfobutylcyclodextrines.

The ratio of the compound of formula (I) or (I') over the water soluble polymer may vary widely. For example ratios of 1/100 to 100/1 may be applied. Interesting ratios of the compound of formula (I) or (I') over cyclodextrin range from about 1/10 to 10/1. More interesting ratios range from about 1/5 to 5/1.

It may further be convenient to formulate the compounds of formula (I) or (I') in the form of nanoparticles which have a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than 1000 nm. Useful surface modifiers are believed to include those which physically adhere to the surface of the compound of formula (I) or (I') but do not chemically bond to said compound.

Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface modifiers include nonionic and anionic surfactants.

Yet another interesting way of formulating the compounds of formula (I) or (I') involves a pharmaceutical composition whereby the compounds of formula (I) or (I') are incorporated in hydrophilic polymers and applying this mixture as a coat film over many small beads, thus yielding a composition which can conveniently be manufactured and which is suitable for preparing pharmaceutical dosage forms for oral administration.

Said beads comprise a central, rounded or spherical core, a coating film of a hydrophilic polymer and a compound of formula (I) or (I') and optionally a seal-coating layer.

Materials suitable for use as cores in the beads are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions and firmness. Examples of such materials are polymers, inorganic substances, organic substances, and saccharides and derivatives thereof.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such unit dosage forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, suppositories, injectable solutions or suspensions and the like, and segregated multiples thereof.

Those of skill in the treatment of HIV-infection could determine the effective daily amount from the test results presented here. In general it is contemplated that an effective daily amount would be from 0.01 mg/kg to 50 mg/kg body weight, more preferably from 0.1 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 1 to 1000 mg, and in particular 5 to 200 mg of active ingredient per unit dosage form.

The exact dosage and frequency of administration depends on the particular compound of formula (I) or (I') used, the particular condition being treated, the severity of the condition being treated, the age, weight and general physical condition of the particular patient as well as other medication the individual may be taking, as is well known to those skilled in the art. Furthermore, it is evident that said effective daily amount may be lowered or increased depending on the response of the treated subject and/or depending on the evaluation of the physician prescribing the compounds of the instant invention. The effective daily amount ranges mentioned hereinabove are therefore only guidelines and are not intended to limit the scope or use of the invention to any extent.

The present compounds of formula (I) or (I') can be used alone or in combination with other therapeutic agents, such as anti-virals, antibiotics, immunomodulators or vaccines for the treatment of viral infections. They may also be used alone or in combination with other prophylactic agents for the prevention of viral infections. The present compounds may be used in vaccines and methods for protecting individuals against viral infections over an extended period of time. The prodrugs may be employed in such vaccines either alone or together with other compounds of this invention or together with other anti-viral agents in a manner consistent with the conventional utilization of reverse transcriptase inhibitors in vaccines. Thus, the present compounds may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective amounts to protect individuals over an extended period of time against HIV infection.

Also, the combination of an antiretroviral compound and a compound of formula (I) or (I') can be used as a medicine. Thus, the present invention also relates to a product containing (a) a compound of formula (I) or (I'), and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in anti-HIV treatment. The different drugs may be combined in a single preparation

together with pharmaceutically acceptable carriers. Said other antiretroviral compounds may be known antiretroviral compounds such as suramine, pentamidine, thymopentin, castanospermine, dextran (dextran sulfate), foscarnet-sodium (trisodium phosphono formate); nucleoside reverse transcriptase inhibitors, e.g. zidovudine (3'-azido-3'-deoxythymidine, AZT), didanosine (2',3'-dideoxyinosine; ddI), zalcitabine (dideoxycytidine, ddC) or lamivudine (2'-3'-dideoxy-3'-thiacytidine, 3TC), stavudine (2',3'-didehydro-3'-deoxythymidine, d4T), abacavir and the like; non-nucleoside reverse transciptase inhibitors such as nevirapine (11-cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-b : 2',3'-e][1,4]diazepin-6-one), efavirenz, delavirdine, TMC-120, TMC-125 and the like; compounds of the TIBO (tetrahydro-imidazo[4,5,1-jk][1,4]-benzodiazepine-2(1*H*)-one and thione)-type e.g. (S)-8-chloro-4,5,6,7-tetrahydro-5-methyl-6-(3-methyl-2-butenyl)imidazo-[4,5,1-jk][1,4]benzodiazepine-2(1*H*)-thione; compounds of the α-APA (α-anilino phenyl acetamide) type e.g. α-[(2-nitrophenyl)amino]-2,6-dichlorobenzene-acetamide and the like; inhibitors of trans-activating proteins, such as TAT-inhibitors, e.g. RO-5-3335, or REV inhibitors, and the like; protease inhibitors *e.g.* indinavir, ritonavir, saquinavir, lopinavir (ABT-378), nelfinavir, amprenavir, TMC-126, BMS-232632, VX-175 and the like; fusion inhibitors, e.g. T-20, T-1249, AMD-3100 and the like; inhibitors of the viral integrase; nucleotide reverse transcriptase inhibitors, e.g. tenofovir and the like; ribonucleotide reductase inhibitors, e.g. hydroxyurea and the like.

By administering the compounds of the present invention with other anti-viral agents which target different events in the viral life cycle, the therapeutic effect of these compounds can be potentiated. Combination therapies as described above exert a synergistic effect in inhibiting HIV replication because each component of the combination acts on a different site of HIV replication. The use of such combinations may reduce the dosage of a given conventional anti-retroviral agent which would be required for a desired therapeutic or prophylactic effect as compared to when that agent is administered as a monotherapy. These combinations may reduce or eliminate the side effects of conventional single anti-retroviral therapy while not interfering with the anti-viral activity of the agents. These combinations reduce potential of resistance to single agent therapies, while minimizing any associated toxicity. These combinations may also increase the efficacy of the conventional agent without increasing the associated toxicity.

The compounds of the present invention may also be administered in combination with immunomodulating agents, e.g. levamisole, bropirimine, anti-human alpha interferon antibody, interferon alpha, interleukin 2, methionine enkephalin, diethyldithiocarbamate, tumor necrosis factor, naltrexone and the like; antibiotics, e.g.

pentamidine isethiorate and the like; or cholinergic agents, e.g. tacrine, rivastigmine, donepezil, galantamine and the like to prevent or combat infection and diseases or symptoms of diseases associated with HIV infections, such as AIDS and ARC, e.g. dementia. A compound of formula (I) or (I') can also be combined with another compound of formula (I) or (I').

Although the present invention focuses on the use of the present compounds for preventing or treating HIV infections, the present compounds may also be used as inhibitory agents for other viruses which depend on similar reverse transcriptases for obligatory events in their life cycle.

The following examples are intended to illustrate the present invention.
Hereinafter, THF means tetrahydrofuran and DMF means *N*,*N*-dimethylformamide.

Experimental part

As described hereinbelow, DMF stands for N,N-dimethylformamide; THF stands for tetrahydrofuran; HPLC stands for High Performance Liquid Chromatography.

Preparation of the intermediate compounds

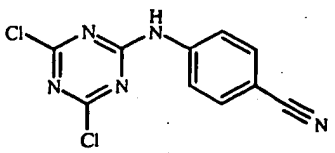
Example A1

a) Reaction under argon flow. A mixture of 4-aminobenzonitrile (0.0210 mol) and diphenyl *N*-cyano-carbonimidate (0.0210 mol) in DMF (25 ml) was stirred for 20 hours at 110°C. Water was added and the resulting precipitate was filtered off, to give a brownish solid. This fraction was recrystallized from CH_3CN. The precipitate was filtered off and dried. Yield : 1.67 g of phenyl *N'*-cyano-*N*-(4-cyanophenyl)-carbamimidate (interm. 1) (30%).

b) Reaction under argon flow. Intermediate (1) (0.00634 mol) was added to a solution of 2,6-dichlorobenzeneethanimidamide (0.00634 mol) in DMF (13 ml). The reaction mixture was stirred for three days at room temperature, then for two days at 60°C. Water was added and the resulting precipitate was filtered off, to give a pure white solid. This fraction was refluxed in CH_3CN (500 ml), cooled and the precipitate was filtered off and dried. Yield : 1.58 g of 4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile (interm. 2) (67%) (mp. 278-279°C).

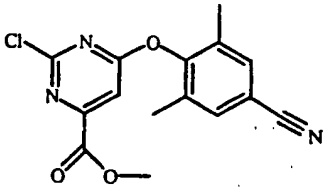
Example A2

a) Preparation of intermediate (3)



Reaction under argon atmosphere. 2,4,6-Trichloro-1,3,5-triazine (0.07440 mol) and THF (100 ml) were combined and cooled to -75°C. Then, 4-aminobenzonitrile (0.07440 mol) was added and the solution was stirred for 4 hours. Then, *N,N*-diethyl-ethanamine (0.07440 mol)) was added dropwise and the reaction mixture was allowed to warm up slowly to room temperature and stirred for 3 days. After adding 1,4-dioxane (100 ml), the resulting precipitate was collected by filtration, washed with THF, and dried. Yield : 12.74 g of intermediate (3).

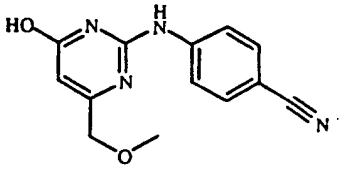
b) Preparation of intermediate (9)



1.6 g (7.73 mmol) of 2-chloro-4-chloro-pyrimidine-6-carboxy methyl ester and 1.19 g (1.05 equiv.) of 4-hydroxy-3,5-dimethyl benzonitrile were dissolved in 20 ml of acetone and 1.28 g (1.2 equiv.) of K_2CO_3 and 58 mg (5 mol%) of NaI were added. The reaction was stirred at 20°C overnight. After that the reaction mixture is cooled to 0°C and filtered off. Acetone is evaporated and the residue is dissolved in ethyl acetate and washed with saturated aqueous $NaHCO_3/H_2O$ 1/1. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was stirred in diisopropyl ether and the product was filtered off, the diisopropyl ether solution was cooled to 0°C and more product was filtered off and dried. Yield : 2.16 g of intermediate (9) (88%).

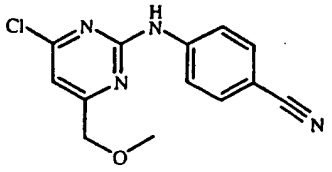
Example A3

Preparation of intermediate (4)



a) Ethanol (140 ml) was dried over sodium and distilled. Ethanol and sodium (0.0611 mol) were combined and stirred until homogeneous. *N*-(4-cyanophenyl)-guanidine monohydrochloride (0.05995 mol) and methyl 4-methoxy-3-oxobutanoate (0.05995 mol) were added. The mixture was stirred and refluxed for 5 hours and cooled to room temperature. The mixture was poured into a mixture of water (450 ml) and HOAc (50 ml). The mixture was stirred for 3 hours, filtered, washed with water, and air dried to produce 10.95 g white solid. The solid was dried at 95°C overnight at 0.2 mm Hg. Yield: 10.19 g of intermediate (4) (66.4%) (264-265°C).

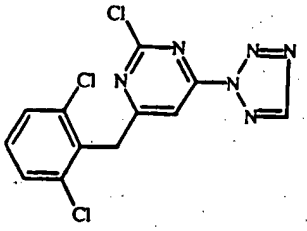
b) Preparation of intermediate (5)



Intermediate (4) (0.0234 mol) was stirred and refluxed in $POCl_3$ (30 ml) for 20 minutes. The mixture was poured onto ice and filtered to yield 10.09 g off-white solid. The sample was dried at 80°C for 16 hours at 0.2 mm Hg. Yield: 6.27 g of intermediate (5) (97.6%) (174-176°C).

Example A4

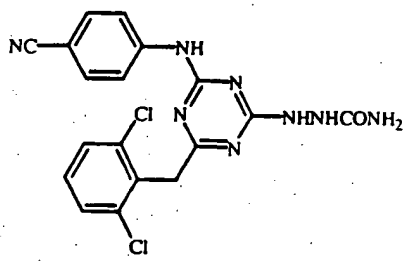
Preparation of intermediate (6)



2,4-Dichloro-6-[(2,6-dichlorophenyl)methyl]pyrimidine (2 mmol), 1H-tetrazole (2 mmol), *N*, *N* -dimethylacetamide (20 ml) and K_2CO_3 (3.6 mol) were combined. The reaction mixture was stirred at 5°C for 2 days. The mixture was poured to 5% HCl (50 ml) and then to ethyl acetate (50 ml). The layers were separated. The organic layer was extracted with brine (50 ml), dried over sodium sulfate, filtered, and the filtrate was concentrated. The product was purified by gradient elution from Silica gel 60 column (0-20% ethyl acetate in hexane). The desired fractions were collected and the solvent was evaporated. White solid was recrystallized from ethanol. Yield : 0.15 g of intermediate (6) (mp.: 167-169°C).

Example A5

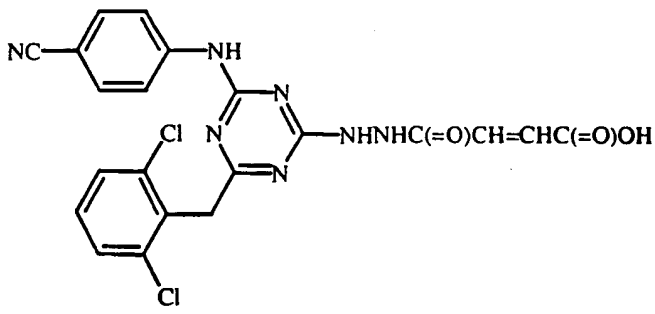
Preparation of intermediate (7)



Hydrazinecarboxamide hydrochloride (0.0013 mol) was dissolved in boiling EtOH (50 ml), then was added NaOH (0.0013 mol), pyridine (0.0013 mol) and compound (1) (0.0013 mol). The mixture was refluxed for 6 hours. White solid obtained was separated via suction, brought in boiling methanol and dioxane and dried. Yield : 0.48 g of intermediate (7) (mp.: 149.5-252°C).

Example A6

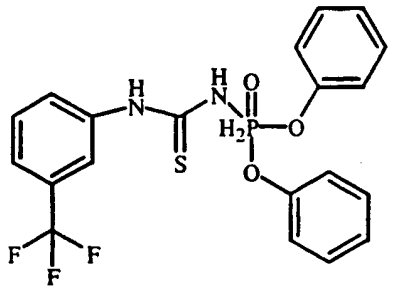
Preparation of intermediate (8)



2,5-Furandione (3 mmol) was added to the solution of 4-[[4-[(2,6-dichlorophenyl)methyl]-6-hydrazino-1,3,5-triazin-2-yl]amino]benzonitrile (A) (2 mmol) in THF (40 ml). The THF solution was stirred for about 2 hours at room temperature. The 100% conversion of (A) to intermediate (8) was confirmed by HPLC. Then THF was removed in vacuum. The raw product was added to absolute ethanol (30 ml) and this heterogenous mixture was refluxed for about 5 minutes. The solid was filtered off, washed with hot chloroform (ca. 20 ml) and dried. Yield: 0.6 g of intermediate (8) (mp.: 229-231°C).

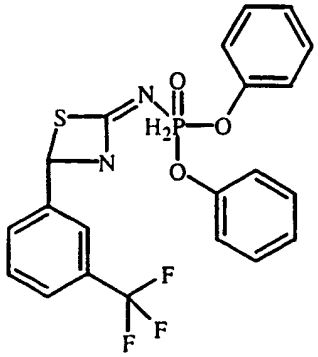
Example A7

a) Preparation of intermediate (10)



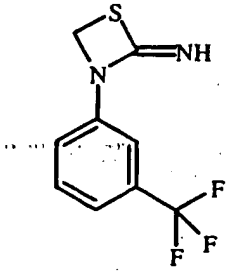
Phosphor(isothiocyanatidic) acid, diphenyl ester (0.155 mol) was stirred in CH_2Cl_2 (300 ml). 3-(trifluoromethyl)-benzenamine (0.155 mol) was added dropwise and the reaction mixture was stirred overnight at room temperature. The mixture was poured out into water and this mixture was stirred for 15 minutes. The layers were separated. The organic layer was washed with water, dried, filtered and the solvent was evaporated. The residue was triturated under diisopropyl ether, filtered off and dried. Yield: 45 g of interm. (10) (64%).

b) Preparation of intermediate (11)



A mixture of interm. (10) (0.0995 mol) and K_2CO_3 (0.4 mol) in 2-propanone (500 ml) was stirred at room temperature. Diiodo-methane (0.2 mol) was added and the reaction mixture was stirred overnight. The mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 99/10. The product fractions were collected and the solvent was evaporated. Yield: 42.3 g of interm. (11) (91.6%).

c) Preparation of intermediate (12)



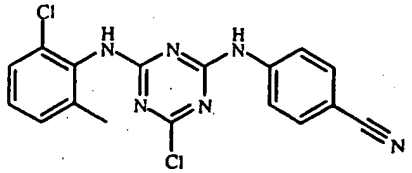
A mixture of interm. (11) (0.069 mol) in HCl 36 % (300 ml) and dioxane (300 ml) was stirred overnight at 40 °C and the solvent was evaporated. The residue was triturated under CH_3CN, filtered off and dried. Yield: 13.8 g of interm. (12) (86.2%).

Preparation of the final compounds

Example B1

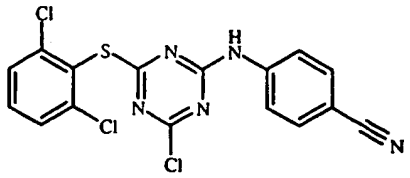
a-1) 2,4-Dichloro-6-[(2,6-dichlorophenyl)methyl]-1,3-5-triazine (0.71 mol) was stirred in toluene (2200 ml) to obtain white suspension (I). *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (124 ml) was added to a suspension of 4-aminobenzonitrile (0.71 mol) in THF (2200 ml), giving solution (II). Solution (II) was added dropwise to (I) over 105 minutes at 24-28°C (water bath). The resulting reaction mixture was stirred overnight at room temperature. Water (2 litre) was added. The separated organic layer was washed twice with water (1.5 litre), and part of the solvent was evaporated. The product crystallized out, was filtered off and dried (vacuum, 40°C, 20 hours). Yield: 235.4 g of 4-[[4-chloro-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]-benzonitrile (85%) (compound 1) (243-244°C).

a-2) Preparation of compound 69

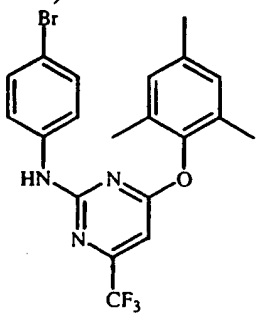


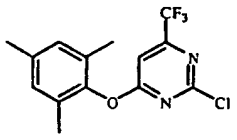
Reaction under argon flow. *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.00714 mol) was added to a solution of 2-chloro-6-methylbenzenamine (0.00714 mol) in 1,4-dioxane (20 ml). A solution of intermediate (3) (0.00714 mol) in 1,4-dioxane (5 ml) was added. The reaction mixture was stirred and refluxed for 24 hours. The solvent was evaporated. CH_2Cl_2 was added. The organic layer was washed with a saturated aqueous

$NaHCO_3$ solution, and the resulting precipitate was filtered off. Yield : 0.56 g of compound 69 (21.1%, white solid).

a-3) Preparation of compound 70 

N-ethyl-*N*-(1-methylethyl)-2-propanamine (0.00752 mol) was added to intermediate (3) (0.00752 mol) in 1,4-dioxane (150 ml), under Argon. 2,6-Dichlorobenzenethiol (0.00752 mol) was added to this mixture, which was then stirred at room temperature for 16 hours. The solvent was evaporated, and the residue was dissolved in ethyl acetate, washed with $NaHCO_3$ and brine, then dried over Na_2SO_4, filtered and the filtrate was evaporated. This fraction was recrystallized from CH_3CN (250 ml). The filtrate from recrystallization was concentrated to approximately 50 ml, cooled, and filtered. Yield : 0.85 g of compound 70 (28%, white solid, used in next reaction step, without further purification) (268-269°C).

a-4) Preparation of compound 24 

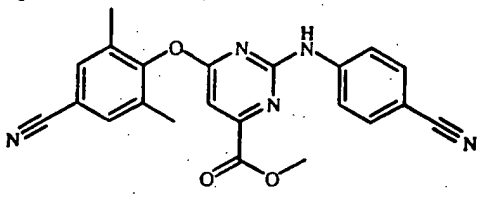
In a flask of 25 ml with magnetic stirring and cooling  (1.9 mmol) and bromoaniline (4.74 mmol) (2.5 eq.) were added in ethanol (5 ml). The mixture was refluxed for 24 hours. The solvent was evaporated. The residu was dissolved in 5 ml ether and 5 ml H_2O. The layers were separated. The aqueous layer was washed 3 times with ether. The organic layers were dried over Na_2SO_4. Yield: 1.2 g of compound 24.

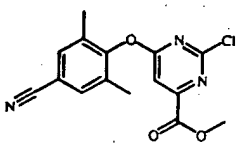
b) Reaction under argon atmosphere. A small portion of 2-(bromomethyl)-1,3-dichloro-benzene in diethylether (40 ml) was added to Mg (0.0813 mol) in diethylether (80 ml). Once the Grignard started to form, the solution of 2-(bromomethyl)-1,3-dichloro-benzene (0.0813 mol) in diethylether (40 ml) was added at a rate that kept the solution refluxing. The solution was stirred at room temperature for 2 hours and, then, added to a solution of 2,4,6-trichloro-1,3,5-triazine (0.0531 mol) in benzene (80 ml) at 0°C. The resulting solution was stirred at 0°C for 1 hour and, then, at room temperature for 2 hours followed by the addition of 4-aminobenzonitrile (0.0542 mol)

in 1,4-dioxane (100 ml). The reaction mixture was stirred at room temperature for 16 hours. Then, *N,N*-diethylethanamine (0.0542 mol) was added, and the reaction mixture was stirred further at room temperature. The reaction mixture was quenched with H_2O, extracted with ethyl acetate, washed with brine (3 x), and dried over K_2CO_3, filtered and the solvent was evaporated. The residue was treated with CH_2Cl_2 and the resulting precipitate was collected by filtration. Yield : 6.99 g of fraction 1 (an off-white solid). The collection of precipitate from subsequent filtrations yielded: 1.80 g of fraction 2 and 1.30 g of fraction 3. Fraction 3 was purified by flash column chromatography over silica gel (eluent: CH_2Cl_2). The desired fractions were collected and the solvent was evaporated. The residue was treated with CH_2Cl_2, filtered off and dried. Yield : 1.47 g of fraction 4.

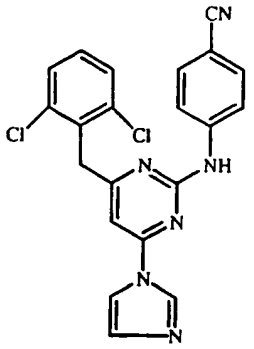
Fractions 1, 2 and 4 were combined and treated with CH_3CN (600 ml). The solvent was evaporated and the residue was dried under vacuum at 80°C and 2.0 mm Hg for 16 hours. The residue was treated with CH_3CN (300 ml), filtered off and dried (2x). The product was dried under vacuum at 100°C and 0.2 mm Hg for 16 hours. Yield : 2.87 g of 4-[[4-chloro-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]-benzonitrile (14.3%); (compound 1) (mp.: 243-244°C).

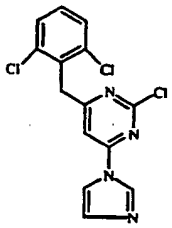
c) Preparation of compound 71

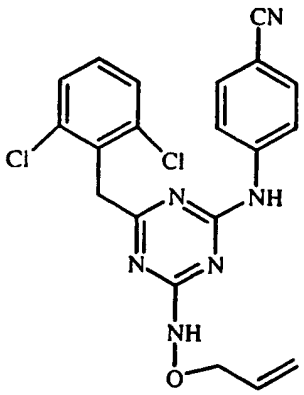


Intermediate (9)  (prepared according to A2b)) (0.00737 mol),

4-aminobenzonitrile (0.01511 mol), and 1-methyl-2-pyrrolidinone (5 ml) were added to a pressure vessel under argon. The mixture was heated at 125-130°C for 7 hours, and the heat was removed. Water, then ether were added. The mixture was stirred and filtered. The filtrate was stirred for 6 hours, and filtered. The filtrate was filtered again. This filtrate was evaporated, then extracted with CH_2Cl_2. This sample was purified by preparative HPLC (gradient of 0.1% trifluoroacetic acid in water and 0.1% trifluoroacetic acid in CH_3CN). Yield: 0.20g of compound 71 (white powder) (mp.: 258-259°C).

d) Preparation of compound 39 

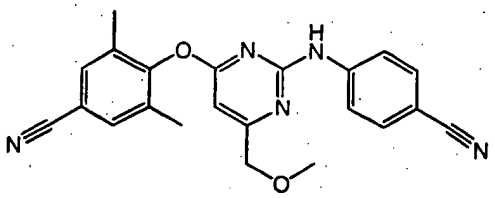
To a solution of  , 4-aminobenzonitrile and 2-methyl-2-propanol in dry dioxane was added catalysator $Pd(PPh_3)_4$. The solution was heated to 100°C with stirring until 2-chloro-4-[(2,6-dichlorophenyl)methyl]-6-(1-imidazolyl)-pyrimidine had been completely consumed. The solution was then cooled to room temperature, taken up in ether (30 ml), and washed with brine (15 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was then suspended in 15% HCl and the solid was filtered off. The crude product was purified by gradient elution from Silica gel 60 column (0-25% acetone in hexane).
Yield: compound 39 (mp.: 275-285°C).

e) Preparation of compound 43 

Compound 1 (0.001 mol) and O-2-propenyl-hydroxylamine (0.0022 mol) were dissolved in 1,4-dioxane (3 ml) in a sealable tube, and NaOH 3M (0.002 mol) was added. The tube was flushed with argon, sealed, and heated for 2 hours to 95 °C, and cooled to room temperature. The solvent was evaporated at 60 °C under a strong nitrogen flow, and the residue was purified by reverse phase HPLC. The product fractions were collected and the solvent was evaporated. Yield: 0.330 g of compound 43 (77.3%, white solid) (mp. :225-227°C).

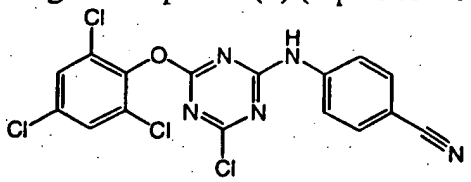
Example B2

a) Preparation of compound 2

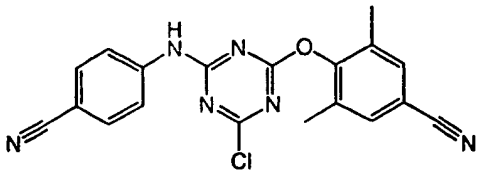


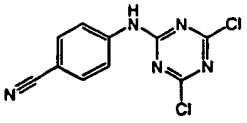
NaH (0.00120 mol) was added to a solution of intermediate (5) (0.00109 mol), 4-hydroxy-3,5-dimethylbenzonitrile (0.00120 mol), 1,4-dioxane (15 ml) and 1-methyl-2-pyrrolidinone (15 ml) in a flask under argon. After the gas evolution ceased, the reaction was heated in an oil bath at 135-140°C for 16 hours. The solvent was evaporated, acetonitrile added, the precipitate filtered and washed with cold CH_3CN to give 3.95 g of fraction 1. The filtrate was filtered to give 0.46 g of fraction 2. The solids were combined and chromatographed on silica gel eluting with 0 and 1% methanol:methylene chloride to give 3.25 g of white solid. This solid was stirred in refluxing CH_3CN and filtered to give 2.56 g of compound (2) (mp.: 203-204°C).

b) Preparation of compound 72

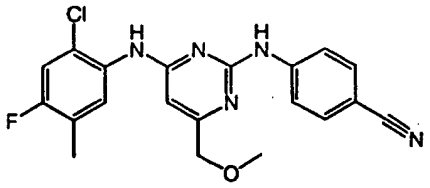


A solution of 2,4,6-trichlorophenol (0.0075 mol) in dry THF (35 ml) was added dropwise over 30 minutes. to a suspension of cleaned NaH (0.0075 mol) in dry THF (5 ml). After 30 minutes of stirring (some effervescence), the mixture was a clear solution, and intermediate (3) (0.0076 mol) was added in one portion followed by additional THF (40 ml). The heterogeneous mixture was stirred over the weekend. More NaH (0.09 g) was added in one portion and the reaction mixture was stirred for 18 hours. The reaction was quenched by pouring into 250 ml of ice. A precipitate formed. The sample and filtrate were treated with ethyl acetate and the layers were separated. The aqueous pH was adjusted with 1 M NaOH and re-extraction was performed. The basic aqueous fraction was then extracted further with ethyl acetate and the combined organic fractions were dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was purified by flash column chromatography over silica gel (eluent: 100% CH_2Cl_2). Two pure fraction groups were collected. The appropriate di-addition fractions were combined to afford 0.28 g of off-white solid which was triturated under diethyl ether, then dried. The appropriate mono-addition fractions were combined and, when needed, recrystallized from ethyl acetate. The obtained residue was purified by chromatography. Yield : 1.28 g of compound 72 (mp.: 238-239°C).

c) Preparation of compound 60 

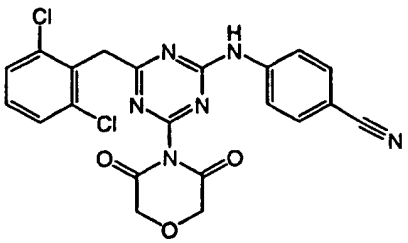
NaOH (0.0036 mol) was added to a solution of 4-hydroxy-3,5-dimethylbenzonitrile in acetone (3.6 ml). The product  was suspended in acetone/H_2O (50 ml). The solution of 4-hydroxy-3,5-dimethylbenzonitrile was added to the suspension and mixed overnight at laboratory temperature. The reaction mixture was diluted with water to 100 ml and neutralised by acetic acid. The crude product was separated by filtration, dried in air and crystallised from chloroform. Yield: 1.04 g (92%) of compound 60 (mp. 260-265°C).

Example B3

Preparation of compound 3 

Reaction in a pressure flask under argon. A mixture of intermediate (5) (0.00364 mol), 2-chloro-4-fluoro-5-methylbenzenamine (0.00401 mol), *N*-ethyl-*N*-(1-methylethyl)-2-propanamine (0.00401 mol) and 1-methyl-2-pyrrolidinone (2 ml) in 1,4-dioxane (3 ml) was heated in an oil bath at 140°C for 3 days. The heat was increased to 160-165°C, and the mixture was heated for 2 days. The heat was increased to 180-185°C, and the mixture was heated for 4 days. The mixture was poured into H_2O, extracted (Et_2O), washed with brine, dried (Na_2SO_4), and evaporated to produce 1.55 g of pale yellow solid. The solid was sonicated in CH_2Cl_2, filtered and recrystallized from CH_3CN to yield 0.32 g of compound (3) (22.1%) (mp.: 213-214°C).

Example B4

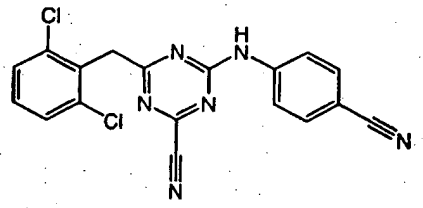
Preparation of compound 4 

1,4-Dioxane-2,6-dione (0.067 mol) and 4-[[4-amino-6-[(2,6-dichlorophenyl)methyl]-1,3,5-triazin-2-yl]amino]benzonitrile (0.00135 mol) were added to a flask and heated in an oil bath while stirring to give a clear solution. The reaction reached 165°C in

15 minutes, and was maintained at 165°C for 35 minutes. The reaction mixture was then removed from the oil bath, cooled to room temperature, then treated between cold water and diethyl ether, using sonication to break up all of the solid mass. The mixture was transferred to a separatory funnel, which gave a quantity of insoluble material. The mixture was suction filtered (collected 0.33 g of white powder) and the filtrate was returned to the funnel. The Et_2O was washed with distilled water until the pH was brought from about 3.0 to neutrality. The mixture was dried over Na_2SO_4 to yield 0.24g of fluffy white wax from the extraction. All material was recombined and purified by flash column chromatography with a solvent coated onto the silica gel using CH_2Cl_2/CH_3CN and a forerun of 250 ml of CH_2Cl_2. The solvent was changed to 95:5 CH_2Cl_2/Et_2O, then 90:10. The desired fractions were collected and the solvent was evaporated. The residue was recrystallized once more. Yield : 0.090 g of compound (4) (14.2%) (mp.: 268-269°C).

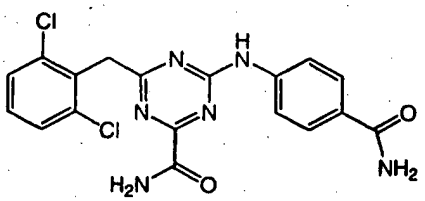
Example B5

a) Preparation of compound 5



A mixture of compound (1) (0.00768 mol), NaCN (0.00971 mol) and $Pd(PPh_3)_4$ (0.0247 mol) in *N,N*-dimethylacetamide (200 ml, freshly distilled) was stirred for 40 minutes at 120°C. The reaction mixture was cooled, poured out into ice-cold water and the resulting precipitate was filtered off, washed with water and dried (vacuum). Some impurities were then removed by double extraction with diethyl ether. This fraction (2.70 g) was purified by column chromatography over silica gel (eluent: CH_2Cl_2/ (CH_3OH/NH_3 satd.) from 100/0 to 90/10). The desired fractions were collected and the solvent was evaporated. Yield : 1.7 g of compound (5) (mp.: 221-230°C).

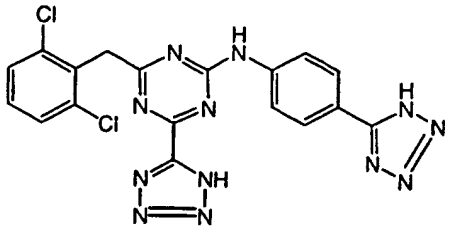
b) Preparation of compound 40



Compound 5 (prepared according to B5a)) was suspended in HCOOH (25 ml) with stirring on a magnetic stirrer. A stream of gas HCL was then passed through the reaction mixture for 1 hour. The mixture was stirred for 20 hours. A product was precipitated by pouring of the reaction mixture into water. Precipitated solid was then

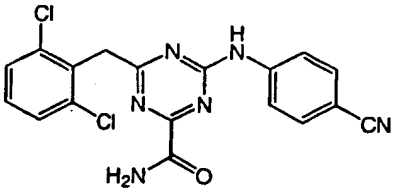
filtered off, washed with water and dried in vacuum dryer. Yield : 4.10 g (89.3%) of compound 40 (mp.: 287-295°C).

c) Preparation of compound 42



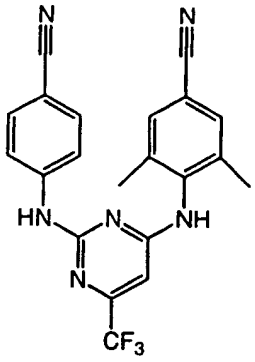
Compound 5 (prepared according to B5a)) (0.0015 mol), NaN_3 (0.030 mol), NH_4Cl (0.030 mol) and *N*, *N*-dimethylacetoacetamide (15 ml) were combined. The reaction mixture was stirred at 140°C for 2 hours. The mixture was poured into 150 ml 5% HCl. The crude product was filtered off, washed with cold water and dried. The product was recrystallized from glacial acetic acid. Yield : 0.67 g (96%) of compound 42 (mp.: 249-252°C).

d) Preparation of compound 38



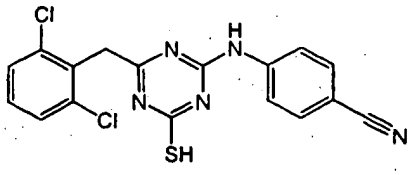
Compound 5 (prepared according B5a)) (5.24 mmol) was suspended in HCOOH (15 ml) with stirring on magnetic stirrer. A stream of gas HCl was then passed through the reaction mixture. The mixture was poured into water after 45 minutes. Precipitated solid was then filtered off, washed with water and dried in vacuum dryer. The crude product (1.91 g) was recrystallized from acetonitrile. Yield : 1.53 g (73.1%) of compound 38 (mp.: 262-263°C).

e) Preparation of compound 33



In a flask of 25 ml equipped with magnetic stirring and cooling compound 32 (prepared according to B1c)) (0.47 mmol) and CuCN (2 eq.) were poured into 1-methyl-2-pyrrolidinone (1 ml). The reaction mixture was heated at 150°C overnight (18 hours.). After cooling, the mixture was diluted with cold H_2O (8 ml) and placed into an icebath for 30 minutes. The precipitate was filtered and washed with ether, carefully triturated and again filtered. Yield : 208 mg of compound 33 (mp.: 249-251°C).

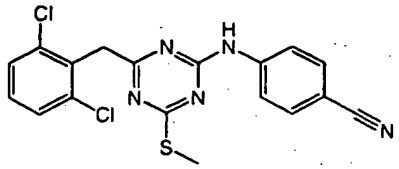
Example B6

Preparation of compound 6 

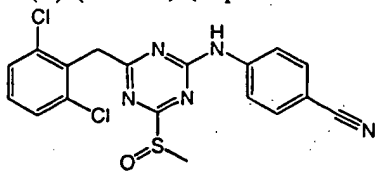
Reaction under argon atmosphere. Sodium sulfide (0.01024 mol) was added to compound (1) (0.00512 mol) in 1,4-dioxane (100 ml). The reaction mixture was stirred at room temperature for three days and the solvent was evaporated. The residue was dissolved in ethyl acetate, washed with 1 N HCl (30 ml), a saturated aqueous sodium bicarbonate solution and with brine, dried with sodium sulfate, filtered, and the solvent was evaporated to give 2.49 g of white solid. This fraction was recrystallized once from acetonitrile to give 0.58 g of fraction 1.

The filtrate was concentrated. The concentrate was cooled and filtered to give 0.59 g of fraction 2. Fractions 1 and 2 were combined and purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0, 99/1 and 98/2). The pure fractions were collected and the solvent was evaporated. The residue was recrystallized from acetonitrile. The precipitate was filtered off and dried (0.2 mm Hg, 80°C, 16 hours). Yield : 0.76 g of compound (6) (38.3%) (mp. 254-255°C).

Example B7

a) Preparation of compound 7 

Reaction under argon atmosphere. A mixture of compound (1) (0.00256 mol) and $NaSCH_3$ (0.00269 mol) in dimethylsulfoxide (10 ml) was stirred for 16 hours at room temperature. Water was added and this mixture was extracted with ethyl acetate. The separated organic layer was washed with brine, dried with potassium carbonate, filtered, and the solvent was evaporated. The residue was crystallized from methanol, then recrystallized from acetonitrile. The sample was dried at 80°C, 0.2 mm Hg for 16 hours. Yield : 0.70 g of compound (7) (68.0%) (mp. 184-185°C).

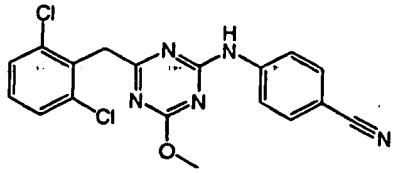
b) Preparation of compound 8 

Reaction under argon atmosphere. 3-Chlorobenzenecarboperoxoic acid (0.00373 mol) was added to a solution of compound (7) (0.00249 mol) in ethanol (150 ml). The reaction mixture was stirred at room temperature for 40 minutes, poured into 600 ml of ice water, extracted two times with ethyl acetate, washed with brine, dried with

potassium carbonate, filtered and the solvent was evaporated to give an off-white solid. The solid was stirred in 2% methanol:methylene chloride (50 ml) and filtered. The filtrate was purified by column chromatography over silica gel (eluent: CH_2Cl_2/CH_3OH 100/0, 99/1 and 98/2). The desired fractions were collected and the solvent was evaporated to give 0.39 g of product. This fraction was recrystallized from methanol. The precipitate was filtered off and dried. The sample was dried at 80°C, 0.2 mm Hg for 16 hours. Yield : 0.20 g of compound (8) (19.2%) (mp. 219-221°C).

Example B8

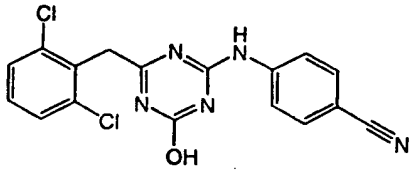
Preparation of compound 9



A suspension of compound (1) (0.0205 mol) in methanol (20 ml) was treated with $LiOCH_3$ (0.0021 mol) in one portion and the heterogeneous reaction mixture was stirred vigorously at room temperature for 28 hours. The reaction mixture was diluted with ether and treated with ice cold 1 M HCl. The layers were separated and the acidic aqueous phase was extracted four more times with ether. The combined ether layers were dried over $MgSO_4/Na_2SO_4$, filtered and the filtrate was evaporated. The residue was recrystallized twice from acetonitrile. The precipitate was filtered off and dried. Yield : 0.43 g of compound (9) (54.3%) (mp. 198-199°C).

Example B9

Preparation of compound 10

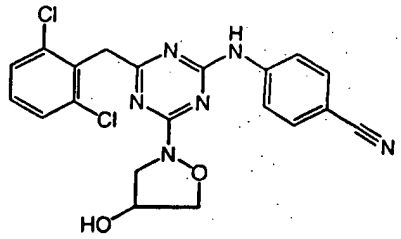


Sodium acetate (0.00463 mol) was added to a solution of compound (1) (0.00153 mol) in dimethylfsulfoxide (15 ml) and the mixture was stirred for 72 hours at room temperature. The reaction mixture was poured into a 100 ml ice-water slurry which caused a voluminous precipitate to form; the mixture was placed in the refrigerator overnight. The precipitate was filtered off, washed extensively with cold water, then dried to give 1.17 g of white solid. This material was powdered and then triturated with ether to give 0.53 g of white powder. One half (0.26 g) of this material was dissolved in pyridine (5 ml) and treated with acetyl chloride (0.07 ml, 0.00098 mol) in one portion. The reaction mixture was stirred at room temperature for 72 hours, then concentrated in vacuo, and extracted between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution. A voluminous solid was insoluble in either fraction. The triphasic mixture

was suction filtered and the collected solid was washed extensively with water, then air-dried. Yield : 0.19 g of compound (10) (mp. >300°C).

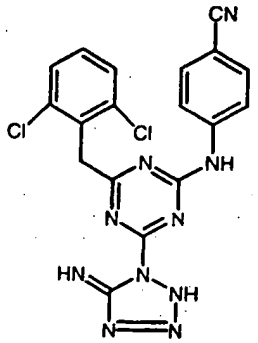
Example B10

a) Preparation of compound 11



Compound (1) (0.00075 mol) and 4-isoxazolidinol HCl (0.0008 mol) were dissolved in 1,4-dioxane (3 ml) in a sealable tube, and NaOH 3M (0.0018 mol) was added. The tube was flushed with nitrogen, sealed, and heated for 3 hours to 90°C, and cooled to room temperature. Methylene chloride (5 ml) and methanol (2 ml) were added, the tube was shaken vigorously, and the bottom (aqueous) layer was removed with a pipette. The organic layer was dried over potassium carbonate, and the tube was centrifuged. The supernatant was separated and evaporated at 50°C under a steady nitrogen flow. The residue was purified by reverse phase HPLC. The pure fractions were collected and the solvent was evaporated. Yield: 0.160 g of compound (11) (49.7%) (mp. 175°C).

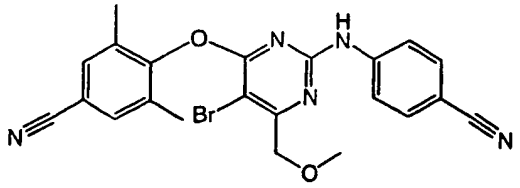
b) Preparation of compound 46



Compound 1 (0.002 mol), 1H-tetrazol-5-amine (0.004 mol), *N*, *N*-dimethylacetamide (6 ml) and K_2CO_3 (0.004 mol) were combined. The reaction mixture was stirred at 120°C for 60 minutes. Mixture was poured into cold water. A product was filtered off, washed with hot water and dried. The product was crystallized from the mixture of tetrahydrofurane/n-heptane. Yield: 0.79 g (90%) of compound 46 (mp.: 302-304°C).

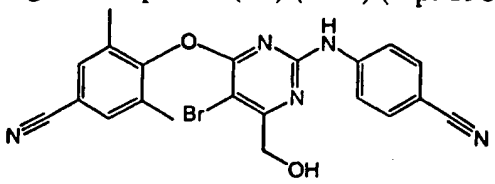
Example B11

a) Preparation of compound 12



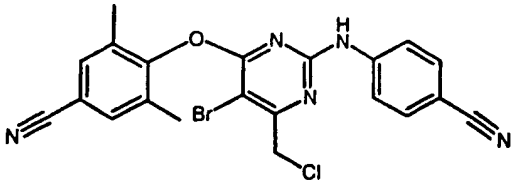
Br_2 (0.12523 mol) was added to a solution of compound (2) (0.00475 mol) and THF (55 ml). After 9 hours, *N,N*-diethylethanamine (1.32 ml), Br_2 (0.22 ml), THF (10 ml), and water (10 ml) were added, and the homogeneous clear solution was stirred overnight. Water (100 ml) was added, and the mixture was extracted (ether), washed (water, brine), and dried (K_2CO_3). The aqueous phase was washed (ether). The ether phase was washed (brine). The organic phases were combined and evaporated to produce 3.75 g white solid. The solid was recrystallized in CH_3CN, dried at 80°C for 16 hours at 0.2 mm Hg to yield 2.19 g of compound (12) (89%) (mp. 198-199°C).

b) Preparation of compound 13



BBr_3 in CH_2Cl_2 (0.01825 mol) was added dropwise over 5 minutes to compound (12) (0.00332 mol) in CH_2Cl_2 (16 ml) under argon at -78°C in a dry ice/2-propanol bath. The mixture was stirred at -78°C for 20 minutes. The bath was replaced with an ice water bath, and the mixture was stirred at 0°C for 50 minutes. Water and CH_2Cl_2 were added until the solution became homogeneous. The organic phase was separated and dried (K_2CO_3). Column chromatography through short path of silica gel (eluent 5% methanol: CH_2Cl_2) produced 1.71 g off-white solid. The solid was taken up in CH_2Cl_2, washed ($NaHCO_3$), dried (Na_2SO_4), and evaporated. The residue was recrystallized in 2-propanol (250 ml) to yield 1.14 g of compound (13) (71.7%) (279-281°C). The solid was dried at 80°C for 4 hours at 0.2 mm Hg.

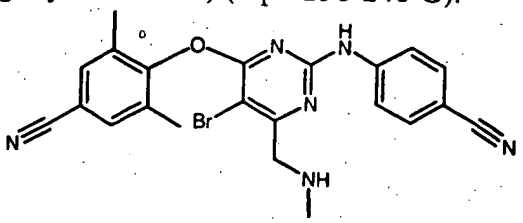
c) Preparation of compound 73



$SOCl_2$ (0.00157 mole) was added to THF (7 ml) and cooled in an ice bath under argon. Compound 13 (prepared according to B11b)) (0.0013 mole) and *N, N*-diethylethanamine (0.0013 mole) were added in THF (10 ml). The reaction was stirred until the ice melted, and the reaction returned to room temperature. $SOCl_2$ (0.100 ml) was added at room temperature, and the reaction was stirred for 2 hours. More $SOCl_2$ (0.05 ml) was added, and the reaction was stirred for 1.5 hours. The mixture was

filtered and the white solid was rinsed with THF. The filtrate was evaporated. Yield 0.600g of compound 73 (97.9%, light yellow solid) (mp.: 238-240°C).

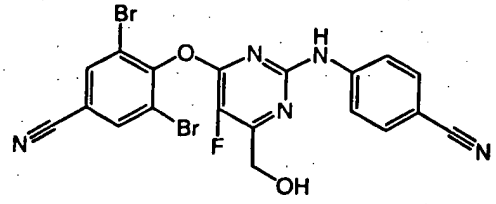
d) Preparation of compound 74



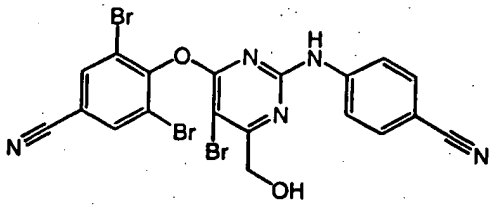
Compound 73 (prepared according to B11c)) (0.000416 mole) was dissolved in methylamine (0.008 mol) in a closed flask and stirred at room temperature for 40 hours. The solvent and excess amine were evaporated. The resulting solid was taken up in ethyl acetate and washed with aqueous $NaHCO_3$ and brine. The organic layer was dried with sodium sulfate and evaporated to give 0.123 g of a yellow solid. The material was recrystallized from ethanol (3x). The solid was dried under vacuum with refluxing toluene overnight. Yield: 0.025g of compound 74 (13%, yellow orange solid) (mp.: 223-224°C).

Example B12

Preparation of

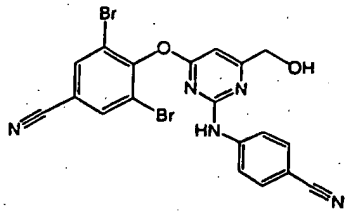


compound 15



compound 16

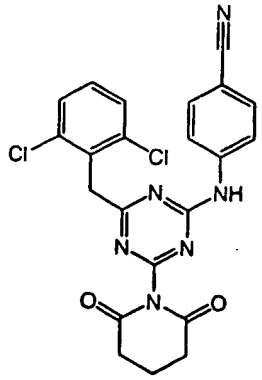
To a flask under argon containing



(0.000639 mol), (compound 14) (prepared according to example B11b)), acetonitrile (10 ml), and $CHCl_3$ (10 mL) was added 1,4-Diazoniabicyclo[2.2.2]octane, 1-(chloromethyl)-4-fluoro-, bis[tetrafluoroborate(1-)] (0.000639 mol). The reaction mixture was refluxed for 15.5 hours, evaporated, dissolved in methylene chloride, washed with water, filtered, dried with potassium carbonate and evaporated. Chromatography on the Gilson Prep LC gave 0.0017 g of compound (15) (0.5%) (240-241°C) and 0.0097 g of compound (16) (2.6%) (m.p.: 250-251°C).

Example B13

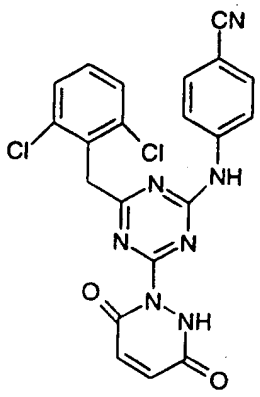
Preparation of compound 37

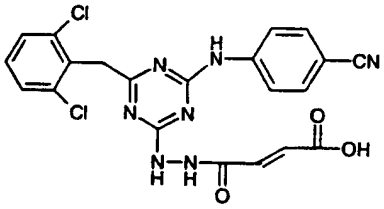


Pentanedioyl dichloride (24 mmol) was added (in portions) to the stirred and refluxed solution of intermediate (2) (6.4 mmol) in dioxane (100 ml). The conversion of intermediate (2) to compound (37) was monitored by HPLC. The reaction mixture was filtered and dioxane was removed in vacuum. The residue obtained was washed with methanol (50 ml) and collected by suction. This solid was purified by slow crystallization from methanol (1000 ml). Yield : 1.09 g (36.5%) of compound (37) (mp. 278-282°C).

Example B14

Preparation of compound 36



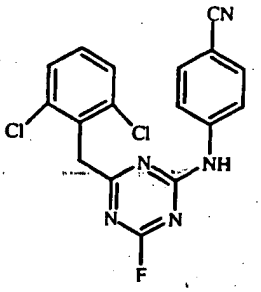


(interm. 8) (2.5 mmol) was added to the suspension of sodium acetate (0.3g) in acetic acid anhydride (12 ml). The mixture was stirred for 30 minutes at 55°C. The reaction was monitored by HPLC. The reaction mixture was poured into a solution of methanol (8 ml) and stirred for 20 minutes. Precipitated solid was collected by suction, washed with methanol (3 ml) and dried. The raw product was extracted with $CHCl_3$ (70 ml). The $CHCl_3$ solution was filtered and concentrated by destillation. Heptane (30 ml) was added to the concentrated

$CHCl_3$ solution (20 ml). The precipitated solid was collected by suction and dried. This solid was finally purified by washing with hot methanol (2 x 10 ml) and hot acetone (1 x 3 ml). The solid was collected by suction and dried. Yield : 0.18 g (16%) of compound 36.

Example B15

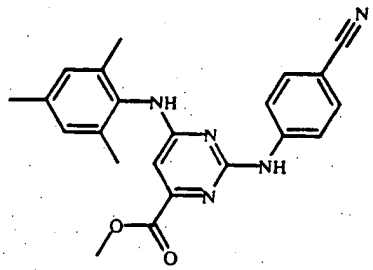
Preparation of compound 49



Compound 1 (0.00512 mol) was dissolved in sulfolane (90 ml)(dried, destilled). KF (0.01455 mol) (freshly burnt) was added at 90°C. Reaction was monitored by HPLC analysis. After 8.5 hours the mixture was cooled to laboratory temperature and poured under good mixing into 500 ml of destilled water. The precipitate was filtered off and mixed with 500 ml of water and the suspension was sonificated and filtered. This procedure was repeated once more. Finally the solid was washed with 150 ml water and dried in the vacuum dryer at 70°C. Yield : 1.87 g of compound 49 (white solid) (mp.: 199-201°C).

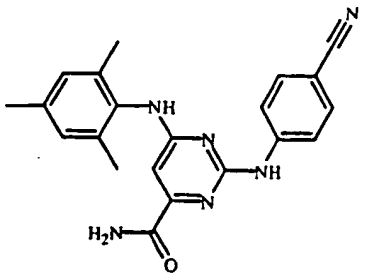
Example B16

a) Preparation of compound 62



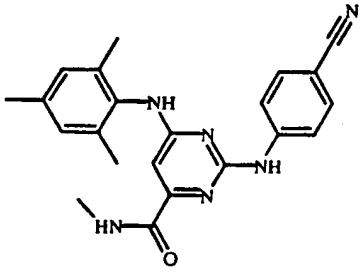
1.00 gram (2.67 mmol) of 2-*N*-(4-cyanoaniline)-4-*N*-(2,4,6-trimethylaniline)pyrimidine-6-carboxylic acid was dissolved in 10 ml of MeOH and 1.13 ml (5 equiv.) of dimethylcarbonate and 40 drops of concentrated H_2SO_4 were added. The reaction mixture was stirred at 65°C for 1 week. After that the reaction was quenched with aqueous saturated $NaHCO_3$ and the MeOH was evaproated. The product was extracted with ethyl acetate and the extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (SiO_2/ethyl acetate) to afford 579 mg (56%) of compound 62.

b) Preparation of compound 61



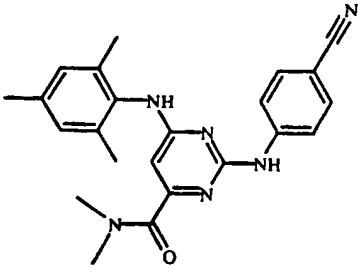
80 mg (0.206 mmol) of compound 62 (prepared according to B16a)) was dissolved in 1.5 ml of dry THF and 1.5 ml of a 7N methanolic solution of NH_3 was added. The mixture was stirred at 20°C overnight. After that the product was filtered off, washed with THF and dried to yield 74 mg (96%) of compound 61.

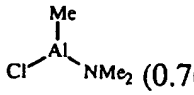
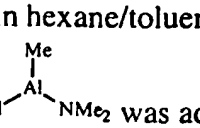
c) Preparation of compound 63



80 mg (0.197 mmol) of compound 62 (prepared according to B16a)) was dissolved in 4 ml THF/MeOH 1/1 and 133 mg (10eq.) of $H_2NMe.HCl$ and 0.5 ml (15 equiv.) of *N,N*-diisopropylethanamine were added. The reaction was stirred overnight at 20°C and after that, the solvents were evaporated. The residue was taken up in ethyl acetate and washed successively with 0.5 N aqueous $KHSO_4$ (2x) and with brine, dried over Na_2SO_4 and evaporated. The residue was stirred in *n*-heptane/diisopropyl ether 1/1 and the product was filtered off and dried to yield 60 mg (75%) of compound 63.

d) Preparation of compound 66

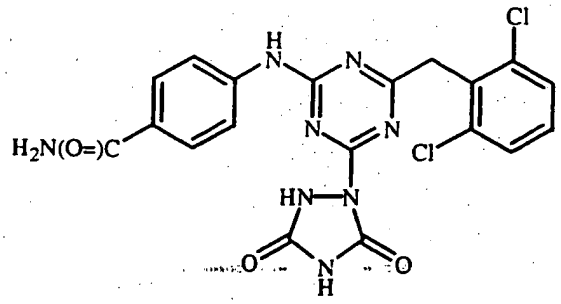


50 mg (0.123 mmol) of compound 62 (prepared according to B16a)) was dissolved in 3 ml of dry THF and 0.200 ml (1.25 equiv.) of  (0.76 M in hexane/toluene) was added. The mixture was stirred overnight at 20°C; 0.050 ml of  was added and the mixture was stirred for another night. After that the THF was evaporated and the residue was taken up in ethyl acetate and washed successively with saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4 and evaporated. The residue was

stirred in *n*-heptane/diisopropyl ether 1/1 and the product was filtered off and dried to yield 44 mg (85%) of compound 66.

Example B17

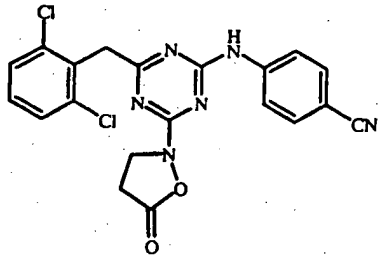
Preparation of compound 41



20 ml of solution $C(=O)Cl_2$ in dioxane (circa 20%) was warmed up to 75°C. Intermediate 7 (prepared according to A5) was added in small portions in 4.5 hours. Content $C(=O)Cl_2$ was checked (aniline) in reaction mixture and excess was maintained by addition of solution $C(=O)Cl_2$. Dioxane was evaporated to dryness and yellow solid was treated with acetone. White solid obtained was filtered and recrystallized from methanol. Yield : 0.87 g (39.3%) of compound 41 (mp.:192-195°C).

Example B18

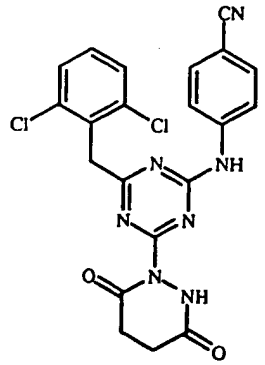
Preparation of compound 35



The mixture of 4-[[4-[(2,6-dichlorophenyl)methyl]-6-(hydroxyamino)-1,3,5-triazin-2-yl]amino]benzonitrile(9 mmol) and THF (50 ml) was stirred and cooled (-12°C). $ClCH_2CH_2C(=O)Cl$ (10.5 mmol) in THF (15 ml) was added dropwise into the previously prepared mixture for about 15 minutes. The solvent was removed by destillation under reduced pressure. The part of raw product was chromatographed on silica gel (CH_2Cl_2/acetone 95:5). The obtained solid was recrystallized from mixture chloroform-heptane (25% chloroform). Yield : 0.1 g (2.5%, white solid) of compound 35 (mp.: 168-173°C).

Example B19

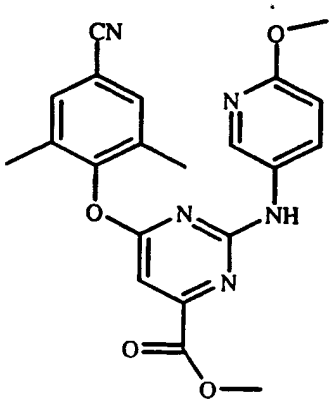
Preparation of compound 34



The mixture of compound 47 (prepared according to B14) (0.4 mmol) in methanol (50 ml) was refluxed and stirred for 5.5 hours. The conversion of compound 47 to compound 34 was monitored by HPLC. The reaction mixture was concentrated by destillation. The precipitated solid was collected by suction and dried.
Yield : 102 mg (55%, white solid) of compound 34 (mp.: 155-157°C).

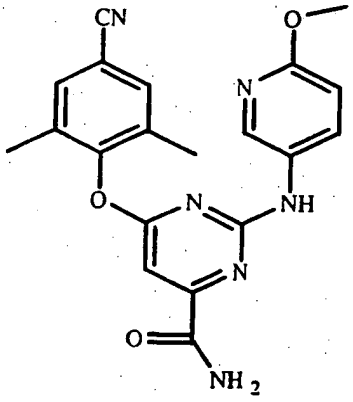
Example B20

a) Preparation of compound 52



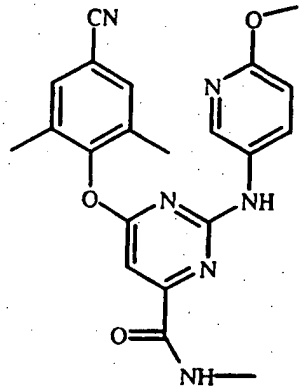
500 mg (1.57 mmol) of interm. (9), 586 mg (3 equiv.) of 5-amino-2-methoxy-pyridine and 47 mg (0.2 mol%) of NaI were dissolved in 10 ml of 1,2-dimethoxy-ethane and stirred at 60°C for 3 days. Then, the mixture was diluted with ethyl acetate and washed succesively with 0.5 N aqueous $KHSO_4$ (2×) and with brine. The organic layer was dried over Na_2SO_4 and evaporated. The residue was purified by silica column chromatography using ethyl acetate/n-heptane 1/1 as the eluent to obtain 306 mg (48%) of compound 52.

b) Preparation of compound 56



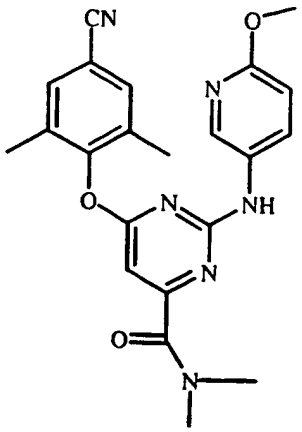
100 mg (0.247 mmol) of compound 52 was dissolved in 2.5 ml of THF and cooled to 0°C. 2.5 ml of a 7 N methanolic NH3 solution was added. The mixture was stirred overnight in a cooler at ± 4°C. The reaction mixture was diluted with diisopropyl ether and evaporated. More diisopropyl ether was added and the mixture was cooled. The product was filtered off to yield 93 mg (96 %) of compound 56.

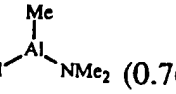
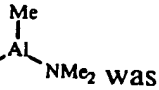
c) Preparation of compound 54



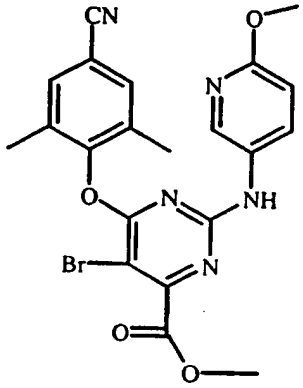
80 mg (o,197 mmol) of compound 52, 133 mg (10 equiv.) of $H_2NMe.HCl$ and 0.5 ml (15 equiv.) of *N*, *N*-diisopropylethanamine were dissolved in 4 ml THF/MeOH 1/1 and stirred overnight at 20°C. After that, the solvents were evaporated and the residue was dissolved in ethyl acetate and washed succesively with 0.5 N $KHSO_4$ (2×) and brine, dried over Na_2SO_4 and evaporated. The residue was stirred in n-heptane/diisopropyl ether 1/1 and the product was filtered off and dried to yield 60 mg (75%) of compound 54.

d) Preparation of compound 65



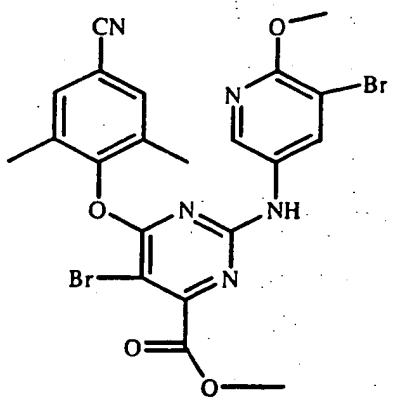
50 mg (o.123 mmol) of compound 52 was dissolved in 3 ml of dry THF and 200 µl (1.25 equiv.) of  (0.76 M in hexane/toluene) was added. The mixture was stirred overnight at 20°C. 50 µl of  was added and stirring was continued for another night. Then, THF was evaporated and the residue was taken up in ethyl acetate and washed successively with saturated aqueous $NaHCO_3$ and with brine, dried over Na_2SO_4 and evaporated. The residue was stirred in n-heptane/diisopropyl ether 1/1 and the product was filtered off and dried to yield 44 mg (85%) of compound 65.

e) Preparation of compound 95



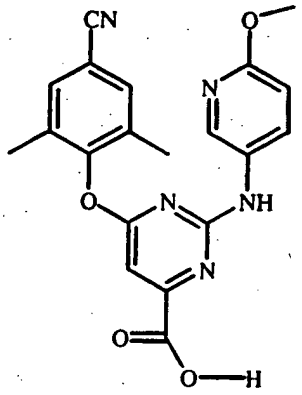
31 mg (o.o765 mmol) of compound 52 was dissolved in 0.73 ml of 0.1 N solution of Br_2 in acetic acid (0.95 equiv.). After overnight stirring at 20°C, the solvent was evaporated and the residue was stirred in ethyl acetate/saturated aqueous $NaHCO_3$ until gas evolution ceased. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was purified by silica preparative thin layer chromatography using ethyl acetate/n-heptane 1/4 as the eluent. The major band is scraped off the thin layer chromatography plate and extracted. The extract was evaporated and dried to yield 21 mg (58%) of compound 95.

f) Preparation of compound 55



20 mg (0.0494 mmol) of compound 52 was suspended in 2 ml of H_2O and 23 mg (3 equiv.) of Br_2 were added. The mixture was stirred at 60°C overnight. Then, the mixture was cooled to 20°C and filtered off. The residue was purified by silica preparative thin layer chromatography using ethyl acetate/n-heptane 1/2 as the eluent. The major band is scraped off the thin layer chromatography plate and extracted. The extract was evaporated and dried to yield 10 mg (36%) of compound 55.

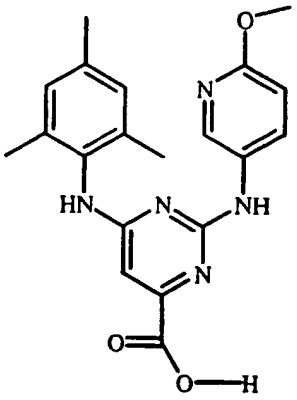
g) Preparation of compound 53



100 mg (0.247 mmol) of compound 52 was dissolved in 7.5 ml of MeOH and 1.75 ml of a 0.4 N aqueous LiOH solution was added. The mixture was stirred at 20°C for 4 hours. Then, Amberlite ion exchange material (H^+-form) was added and 2 ml of MeOH. When the solution was neutral, the Amberlite was filtered off, MeOH was evaporated and the residue was stirred in diisopropyl ether, filtered off and dried to yield 80 mg (83%) of compound 53.

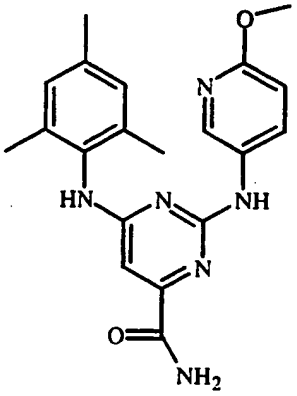
Example B21

a) Preparation of compound 50



200 mg (0.654 mmol) of 2-chloro-4-N-(2,4,6-trimethylanilinyl)-pyrimidine-6-carboxy methyl ester, prepared according to A2a), and 244 mg (3 equiv.) of 5-amino-2-methoxy-pyridine were dissolved in 2 ml of n-BuOH and 2 ml of H_2O and 3 drops of 37 % aqueous HCl were added. The reaction mixture was stirred at 85°C for 2 days. Then, the solvents were evaporated, the residue was stirred in 15 ml H_20/15 ml CH_2Cl_2 and the solid material was filtered off. The residue was washed with H_2O, with diethyl ether and with CH_2Cl_2 to yield 127 mg (51%) of compound 50.

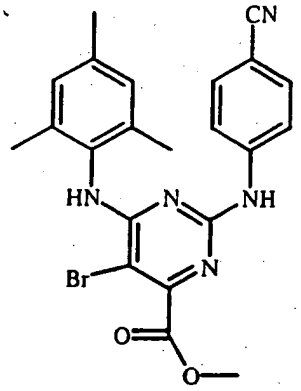
b) Preparation of compound 51



60 mg (0.158 mmol) of compound 50 was suspended in dry DMF and 58 µl (5 equiv.) of $SOCl_2$ were added. The reaction mixture was stirred at 60°C overnight and the excess $SOCl_2$ was removed by evaporation. The DMF solution was cooled to 0°C and 2 ml of 37°C NH_4OH was added. The reaction mixture was stirred for 1 hour at 0°C. Then, the solvents were evaporated and the residue was stirred in MeOH for 2 hours, filtered off and washed with diisopropyl ether to yield 30 mg (50%) of compound 51.

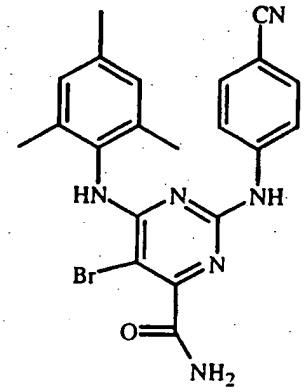
Example B22

a) Preparation of compound 96



60 mg (0.155 mmol) of compound 62, prepared according to B16a), was dissolved in 1.7 ml of 0.1 N solution of Br_2 in acetic acid (1.1 equiv.). After 1 hour, the solvent was evaporated and the residue was stirred in ethyl acetate/saturated aqueous $NaHCO_3$ until gas evolution ceased. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated. The residue was stripped with n-heptane and stirred in n-heptane /diisopropyl ether 1/1 and the product was filtered off and dried to yield 72 mg (100%) of compound 96.

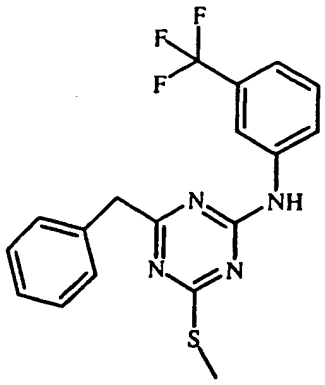
b) Preparation of compound 98



105 mg (0.225 mmol) of compound 96 was dissolved in 2 ml of MeOH and 2 ml of a 7 N NH_3 solution in MeOH was added. The reaction was stirred at 20°C over the weekend. The solvent was evaporated and the residue stripped with CH_2Cl_2, stirred in diisopropyl ether and filtered off to yield 64 mg (63%) of compound 98.

Example B23

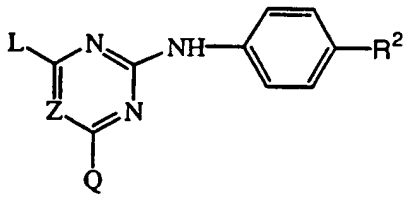
Preparation of compound 93



A mixture of interm. 12 (0.00028 mol) and benzeneacetyl chloride (0.00028 mol) in acetonitrile (10 ml) was stirred while cooling on an ice-bath. Sodium acetate (0.00084 mol) was added and the mixture was stirred for 30 minutes on an ice-bath, then stirred overnight at room temperature. Methyl carbamimidothioate (0.00056 mol) was added. Na_2CO_3 (0.0011 mol) was added and the mixture was stirred overnight at 80 °C, then cooled to room temperature. CH_2Cl_2 (10 ml) was added. Water (2 ml) was added and the mixture was stirred for 30 minutes. The mixture was filtered through Extrelut and the filtrate was evaporated. The residue was purified by HPLC over silica gel (eluent: CH_2Cl_2/CH_3OH 90/10). The product fractions were collected and the solvent was evaporated to yield compound 93.

The following Tables list compounds of formula (I) as prepared according to one of the above examples (Ex. No.).

Table 1



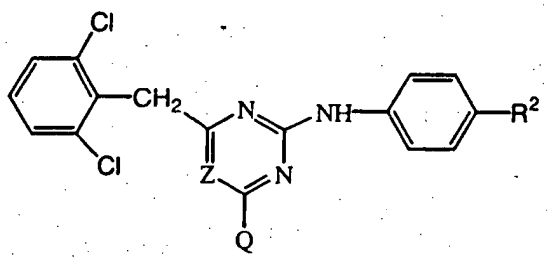
Co. No.	Ex. No.	Z	R^2	L	Q	Physical data/mp.
17	B1a-2	CH	Br	(2,4,6-trimethylphenyl)amino	CF_3	198-201°C
18	B5a	N	CN	(2,4,6-trimethylphenyl)amino	CN	309-313°C
19	B5d	N	CN	(2,4,6-trimethylphenyl)amino	$C(=O)-NH_2$	
20	B7	N	CN	(2,4,6-trimethylphenyl)amino	SCH_3	108-109°C
21	B5e	CH	CN	(2,4,6-trimethylphenyl)amino	CF_3	179-182°C
22	B21a	CH	CN	(2,4,6-trimethylphenyl)amino	COOH	

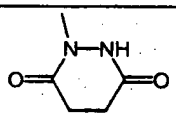
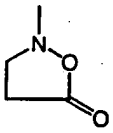
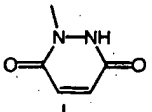
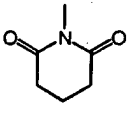
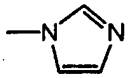
Co. No.	Ex. No.	Z	R^2	L	Q	Physical data/mp.
23	B5a	N	CN	(2,4,6-trimethylphenyl)oxy	CN	
24	B1a-4	CH	Br	(2,4,6-trimethylphenyl)oxy	CF_3	129°C
25	B5e	CH	CN	(2,4,6-trimethylphenyl)oxy	CF_3	202°C
26	B5d	N	CN	(2,4,6-trimethylphenyl)oxy	$C(=O)-NH_2$	280-286°C
27	B2	CH	CN	(2,6-dibromo-4-cyano phenyl)oxy	CH_2-O-CH_3	218-220°C
14	B12	CH	CN	(2,6-dibromo-4-cyano phenyl)oxy	CH_2-OH	277-278°C
15	B12	C-F	CN	(2,6-dibromo-4-cyano phenyl)oxy	CH_2-OH	240-241°C
16	B12	C-Br	CN	(2,6-dibromo-4-cyano phenyl)oxy	CH_2-OH	250-251°C
28	B5	N	CN	(4-cyano-2,6-dimethyl phenyl)oxy	CN	288-291.5°
29	B5e	CH	CN	(2,6-dimethylphenyl)amino	CF_3	
30	B5e	CH	CN	(2,6-dimethylphenyl)oxy	CF_3	
31	B1a-4	CH	Br	(2,6-dimethylphenyl)oxy	CF_3	
3	B3	CH	CN	(2-chloro-4-fluoro-5-methyl-phenyl)amino	CH_2-O-CH_3	213-214°C
32	B1c	CH	CN	(4-bromo-2,6-dimethyl-phenyl)amino	CF_3	209-211°C
33	B5e	CH	CN	(4-cyano-2,6-dimethyl-phenyl)amino	CF_3	249-251°C
2	B2	CH	CN	(4-cyano-2,6-dimethyl phenyl)oxy	CH_2-O-CH_3	203-204°C
12	B11a	C-Br	CN	(4-cyano-2,6-dimethyl phenyl)oxy	CH_2-O-CH_3	198-199°C
13	B11b	C-Br	CN	(4-cyano-2,6-dimethyl phenyl)oxy	CH_2-OH	279-281°C
57	B2b	N	CN	(2,4,6-trimethylphenyl)oxy	Cl	234-236°C
60	B2c	N	CN	(4-cyano-2,6-dimethyl phenyl)oxy	Cl	260-265°C
61	B16b	CH	CN	(2,4,6-trimethylphenyl)amino	$C(=O)-NH_2$	
62	B16a	CH	CN	(2,4,6-trimethylphenyl)amino	$C(=O)-OCH_3$	
63	B16c	CH	CN	(2,4,6-trimethylphenyl)amino	$C(=O)-NHCH_3$	
66	B16d	CH	CN	(2,4,6-trimethylphenyl)amino	$C(=O)-N(CH_3)_2$	
67	B1a-2	N	CN	(2,4,6-trimethylphenyl)amino	Cl	275-276°C
79	B1a-2	N	CN	(2,6-ethylphenyl)amino	Cl	

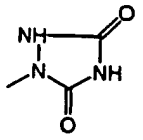
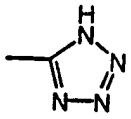
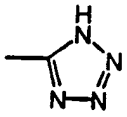
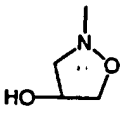
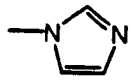
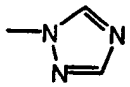
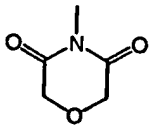
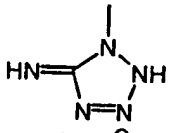
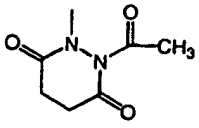
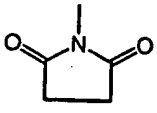
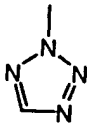
Co. No.	Ex. No.	Z	R^2	L	Q	Physical data/mp.
80	B1a-2	N	CN	(2-oxomethyl-5-methyl-phenyl)amino	Cl	
81	B1a-2	N	CN	(4-bromo-2,6-dimethyl-phenyl)amino	Cl	
82	B1a-2	N	CN	(5-bromo-2,4,6-trimethyl-phenyl)amino	Cl	
83	B1a-2	N	CN	(2-ethyl-6-methylphenyl)amino	Cl	
84	B1a-2	N	CN	(2-broom-4,6-difluoro-phenyl)amino	Cl	
85	B1a-2	N	CN	(2,4,6-trichlorophenyl)amino	Cl	295-296°C
70	B1a-3	N	CN	(2,6-dichlorophenyl)amino	Cl	268-269°C
86	B1a-2	N	CN	(2,6-dichloro-4-trifluoromethyl-phenyl)amino	Cl	247-248°C
87	B1a-2	N	CN	(2,4-dichloro-6-trifluoromethyl-phenyl)amino	Cl	275-276°C
88	B1a-2	N	CN	(2,4,6-tribromophenyl)amino	Cl	292-294°C
89	B1a-2	N	CN	(2,6-dibromo-4-methyl-phenyl)amino	Cl	283-284°C
90	B1a-2	N	CN	(2,6-dibromo-4-*i*propyl-phenyl)amino	Cl	263-264°C
91	B1a-2	N	OCH_3	(4-methoxyphenyl)amino	Cl	
96	B22a	C-Br	CN	(2,4,6-trimethylphenyl)amino	$COOCH_3$	
71	B1c	CH	CN	(4-cyano-2,6-dimethyl-phenyl)amino	$COOCH_3$	258-259°C
97	B1c	CH	CN	(4-cyano-2,6-dimethyl-phenyl)amino	COOH	258-259°C
98	B22b	C-Br	CN	(2,4,6-trimethylphenyl)amino	$CONH_2$	
73	B11c	C-Br	CN	(4-cyano-2,6-dimethyl-phenyl)amino	CH_2Cl	238-240°C
74	B11d	C-Br	CN	(4-cyano-2,6-dimethyl-phenyl)oxy	CH_2NHCH_3	223-224°C
100	B11d	C-Br	CN	(4-cyano-2,6-dimethyl-phenyl)oxy	$CH_2N(CH_3)_2$	189-191°C
101	B11d	C-Br	CN	(4-cyano-2,6-dimethyl-phenyl)oxy	CH_2NHCH_2CH	202-203°C

Co. No.	Ex. No.	Z	R^2	L	Q	Physical data/mp.
103	B2a	N	CN	(2,6-dichlorophenyl)oxy	Cl	
104	B1b	N	CN	(2-chloro-4-fluorophenyl)methyl	Cl	201-202°C
105	B1b	N	CN	(2,4-dichlorophenyl)methyl	Cl	191-192°C
106	B1a	N	CN	(2,6-dichlorophenyl)amino	Cl	
107	B1a-1	N	CN	(2,6-dimethylphenyl)amino	Cl	
69	B1a-2	N	CN	(2-chloro-6-methylphenyl)amino	Cl	
108	B1a-2	N	CN	(2-*i*propyl-6-methyl-phenyl)amino	Cl	
109	B1a-2	N	CN	(2,4-dichloro-6-methyl-phenyl)amino	Cl	
110	B1a-2	N	CN	(3-chloro-2,6-dimethyl-phenyl)amino	Cl	142-143°C
72	B2b	N	CN	(2,4,6-trichlorophenyl)oxy	Cl	238-239°C

Table 2



Co. No.	Ex. No.	Z	R^2	Q	Physical data mp.
34	B19	N	CN		155-157°C
35	B18	N	CN		168-173°C
36	B14	N	CN		
37	B13	N	CN		278-282°C
38	B5d	N	CN	C(=O)-NH_2	262-263°C
39	B1d	CH	CN		275-285°C
5	B5	N	CN	CN	221-230°C

Co. No.	Ex. No.	Z	R^2	Q	Physical data mp.
40	B5b	N	$C(=O)-NH_2$	$C(=O)-NH_2$	287-295°C
41	B17	N	$C(=O)-NH_2$		192-195°C
42	B5c	N			249-252°C
11	B10a	N	CN		.trifluoroacetate (1:1); 175°C
1	B1	N	CN	Cl	243-244°C
7	B7a	N	CN	$S-CH_3$	184-185°C
8	B7b	N	CN	$S(=O)-CH_3$	219-221°C
9	B8	N	CN	OCH_3	198-199°C
6	B6	N	CN	SH	254-255°C
10	B9	N	CN	OH	>300°C
44	B10b	N	CN		
45	B10b	N	CN		267-270°C
4	B4	N	CN		268-269°C
46	B10b	N	CN		302-304°C
47	B14	N	CN		213-215°C
48	B13	N	CN		223-226°C
49	B15	N	CN	F	196°C
58	B8	N	CN	OC_2H_5	302-304°C
59	B10a	N	CN		196-197°C
43	B1e	N	CN	$NH-O-CH_2-C=CH$	trifluoroacetate (1:1); 225-227°C

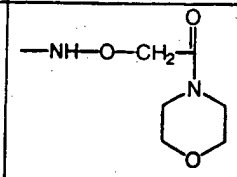
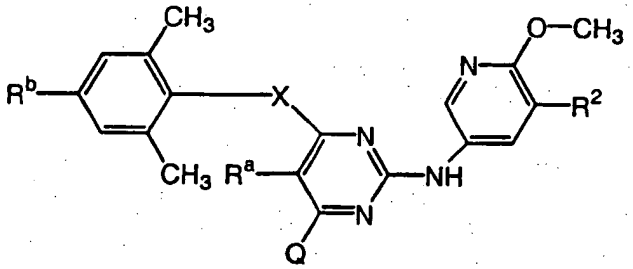
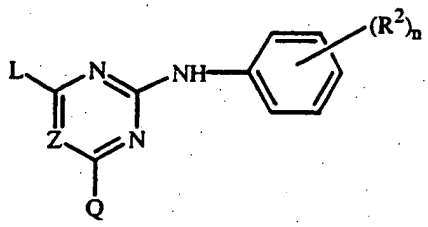
Co. No.	Ex. No.	Z	R^2	Q	Physical data mp.
68	B1e	N	CN		trifluoroacetate (1:1); >80°C

Table 3



Co. No.	Ex. No.	X	R^a	R^b	R^2	Q	Physical data
50	B21a	NH	H	CH_3	H	COOH	
51	B21b	NH	H	CH_3	H	$C(=O)-NH_2$	
52	B20a	O	H	CN	H	$COOCH_3$	
53	B20g	O	H	CN	H	COOH	
54	B20c	O	H	CN	H	$C(=O)-NH-CH_3$	
55	B20f	O	Br	CN	Br	$COOCH_3$	
56	B20b	O	H	CN	H	$C(=O)-NH_2$	
65	B20d	O	H	CN	H	$C(=O)-N(CH_3)_2$	
95	B20e	O	Br	CN	H	$COOCH_3$	

Table 4



Co. No.	Ex. No.	Z	R^2	L	Q	Physical data/mp.
92	B23	N	2,3-dichloro	benzyl	SCH_3	
93	B23	N	3-trifluoromethyl	benzyl	SCH_3	
94	B23	N	3-trifluoromethyl	benzyl	OCH_3	

C. Pharmacological example

The pharmacological activity of the present compounds was examined using the following test.

A rapid, sensitive and automated assay procedure was used for the *in vitro* evaluation of anti-HIV agents. An HIV-1 transformed T4-cell line, MT-4, which was previously shown (Koyanagi et al., *Int. J. Cancer*, 36, 445-451, 1985) to be highly susceptible to and permissive for HIV infection, served as the target cell line. Inhibition of the HIV-induced cytopathic effect was used as the end point. The viability of both HIV- and mock-infected cells was assessed spectrophotometrically via the *in situ* reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT). The 50% cytotoxic concentration (CC_{50} in μM) was defined as the concentration of compound that reduced the absorbance of the mock-infected control sample by 50%. The percent protection achieved by the compound in HIV-infected cells was calculated by the following formula :

$$\frac{(OD_T)_{HIV} - (OD_C)_{HIV}}{(OD_C)_{MOCK} - (OD_C)_{HIV}} \quad \text{expressed in \%,}$$

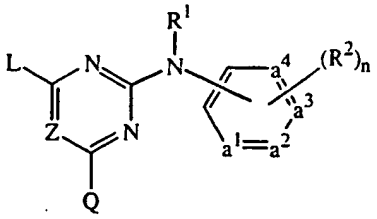
whereby $(OD_T)_{HIV}$ is the optical density measured with a given concentration of the test compound in HIV-infected cells; $(OD_C)_{HIV}$ is the optical density measured for the control untreated HIV-infected cells; $(OD_C)_{MOCK}$ is the optical density measured for the control untreated mock-infected cells; all optical density values were determined at 540 nm. The dose achieving 50% protection according to the above formula was defined as the 50% inhibitory concentration (IC_{50} in μM). The ratio of CC_{50} to IC_{50} was defined as the selectivity index (SI). Table 5 lists the IC_{50}, CC_{50} and SI values for the compounds of formula (I).

Table 5

Co. No.	IC_{50} (μM)	CC_{50} (μM)	SI
7	0.02	39.81	1990
9	0.01	>100	>10000
67	0.001995	>10	>5012
4	0.00158	39.81	25197
48	0.0079	>200	>12658
25	0.079	>100	>1266
20	0.002	3.981	1990
58	0.0251	50.12	1997
35	0.0631	50.12	794
33	0.00316	5.012	1586
38	0.00251	>100	>39841
5	0.01995	10	501
43	0.01585	63.096	3981
11	0.00251	63.096	25138
68	0.01585	19.95	1259
19	0.001259	3.981	3162
2	0.001585	50.12	31621
12	0.0040	>100	>25000
13	0.0040	>100	>25000
26	0.001	1.995	1995
3	0.0501	>100	>1996
27	0.01	>10	>1000
14	0.0040	>10	2500
56	0.0631	>100	1585
16	0.0251	>100	>39841
65	0.07943	79.43	1000
62	0.0063	7.943	1261
61	0.00251	50.12	19968
63	0.00501	39.81	7946
66	0.001585	31.62	19950
71	0.0251	>100	>3984
109	0.00398	12.59	3163
85	0.02	50.12	2506
89	0.00501	10	1996
98	0.00316	50.12	15861

Claims

1. A compound of formula



(I)

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

$-a^1=a^2-a^3=a^4-$ represents a bivalent radical of formula

-CH=CH-CH=CH- (a-1);

-N=CH-CH=CH- (a-2);

-N=CH-N=CH- (a-3);

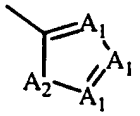
-N=CH-CH=N- (a-4);

-N=N-CH=CH- (a-5);

n is 0, 1, 2, 3 or 4; and in case $-a^1=a^2-a^3=a^4-$ is (a-1), then n may also be 5;

R^1 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or $-C(=O)R^6$, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, $-S(=O)_pR^6$, $-NH-S(=O)_pR^6$, $-C(=O)R^6$, -NHC(=O)H, $-C(=O)NHNH_2$, $-NHC(=O)R^6$, $-C(=NH)R^6$ or a radical of formula



(c)

wherein each A_1 independently is N, CH or CR^6; and

A_2 is NH, O, S or NR^6;

L is C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said groups may be substituted with one or two substituents independently selected from

* C_{3-7}cycloalkyl,
* indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy,

C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl,

* phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; or

L is $-X^1-R^3$ or $-X^2$-Alk-R^4 wherein

Alk is C_{1-4}alkanediyl;

R^3 or R^4 each independently are phenyl, pyridyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2; and

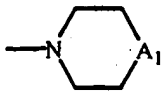
X^1 or X^2 each independently are $-NR^7-$, -NH-NH-, -N=N-, -O-, -C(=O)-, -CHOH-, -S-, $-S(=O)_p-$;

Q represents cyano, hydroxy, mercapto, carboxyl, formyl, halo, cyanoC_{1-6}alkyl, hydroxyC_{1-6}alkyl, mercaptoC_{1-6}alkyl, aminoC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)-aminoC_{1-6}alkyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, C_{1-6}alkyl-oxy, C_{1-6}alkylthio, C_{1-6}alkyl$S(=O)_p$, C_{1-6}alkylcarbonyl, C_{1-6}alkylcarbonyloxy, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyloxyC_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkenyl-oxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, C_{2-6}alkynyl, polyhaloC_{1-6}alkyl, hydroxy-polyhaloC_{1-6}alkyl, Het or C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy;

Z is C-Y or N wherein

Y represents hydrogen, hydroxy, halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms, C_{2-6}alkynyl optionally substituted with one or more halogen atoms, C_{1-6}alkyl substituted with cyano or $-C(=O)R^8$, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalo-methylthio, $-S(=O)_pR^8$, $-NH-S(=O)_pR^8$, $-C(=O)R^8$, -NHC(=O)H, $-C(=O)NHNH_2$, $-NHC(=O)R^8$, $-C(=NH)R^8$ or aryl;

R^5 is hydrogen or a radical of formula



(d)

with A_1 being CH_2 or O;

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

R^7 is hydrogen; aryl; formyl; C_{1-6}alkylcarbonyl; C_{1-6}alkyl; C_{1-6}alkyloxycarbonyl; C_{1-6}alkyl substituted with formyl, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl,

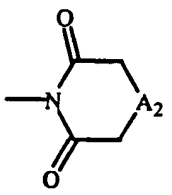
C_{1-6}alkylcarbonyloxy; C_{1-6}alkyloxyC_{1-6}alkylcarbonyl substituted with C_{1-6}alkyloxycarbonyl;

R^8 is methyl, amino, mono- or dimethylamino or polyhalomethyl;

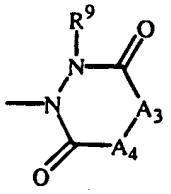
p is 1 or 2;

aryl is phenyl or phenyl substituted with one, two, three, four or five substituents each independently selected from halo, C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{1-6}alkyloxy, cyano, nitro, polyhaloC_{1-6}alkyl, polyhaloC_{1-6}alkyloxy, aminocarbonyl, tetrazolyl;

Het is imidazolyl, thiazolyl, oxazolyl, pyrazolyl, isothiazolyl, isoxazolyl, triazolyl, tetrazolyl optionally substituted with imino, a radical of formula (c) as described hereinabove, imidazolidinyl, pyrazolidinyl, thiazolidinyl, isothiazolidinyl, oxazolidinyl, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone, or a radical of formula



(e-1)



(e-2)

with A_2 being O, CH_2 or a direct bond;

A_3 being CH_2 or NH;

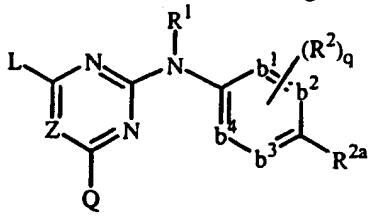
A_4 being CH_2 or a direct bond; or

A_3-A_4 representing CH=CH;

R^9 being hydrogen or C_{1-4}alkylcarbonyl;

provided that when Q is halo then Z is N; or when Q is polyhaloC_{1-6}alkyl then Y is hydrogen or C_{1-6}alkyl.

2. A compound as claimed in claim 1 having the formula



(I')

a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof, wherein

$-b^1=b^2-C(R^{2a})=b^3-b^4=$ represents a bivalent radical of formula

$-CH=CH-C(R^{2a})=CH-CH=$ (b-1);

$-N=CH-C(R^{2a})=CH-CH=$ (b-2);

$-CH=N-C(R^{2a})=CH-CH=$ (b-3);

$-N=CH-C(R^{2a})=N-CH=$ (b-4);

-N=CH-C(R^{2a})=CH-N= (b-5);

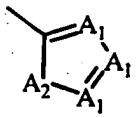
-CH=N-C(R^{2a})=N-CH= (b-6);

-N=N-C(R^{2a})=CH-CH= (b-7);

q is 0, 1, 2; or where possible q is 3 or 4;

R^{2a} is cyano, aminocarbonyl, mono- or di(methyl)aminocarbonyl, C_{1-6}alkyl substituted with cyano, aminocarbonyl or mono- or di(methyl)aminocarbonyl, C_{2-6}alkenyl substituted with cyano, or C_{2-6}alkynyl substituted with cyano;

each R^2 independently is hydroxy, halo, C_{1-6}alkyl optionally substituted with cyano or -C(=O)R^6, C_{3-7}cycloalkyl, C_{2-6}alkenyl optionally substituted with one or more halogen atoms or cyano, C_{2-6}alkynyl optionally substituted with one or more halogen atoms or cyano, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, cyano, nitro, amino, mono- or di(C_{1-6}alkyl)amino, polyhalomethyl, polyhalomethyloxy, polyhalomethylthio, -S(=O)$_p$$R^6$, -NH-S(=O)$_p$$R^6$, -C(=O)$R^6$, -NHC(=O)H, -C(=O)$NHNH_2$, -NHC(=O)$R^6$,-C(=NH)$R^6$ or a radical of formula



(c)

wherein each A_1 independently is N, CH or CR^6;

A_2 is NH, O, S or NR^6;

p is 1 or 2;

R^6 is methyl, amino, mono- or dimethylamino or polyhalomethyl; and

wherein L, Q, Z, and R^1 are defined as in claim 1.

3. A compound as claimed in claim 1 or 2 wherein Q is cyano, hydroxy, mercapto, carboxyl, hydroxyC_{1-6}alkyl, mono- or di(C_{1-4}alkyl)aminoC_{1-6}alkyl, aminocarbonyl, C_{1-6}alkyloxyC_{1-6}alkyl wherein each hydrogen atom may optionally be substituted with C_{1-6}alkyloxy, C_{1-6}alkyloxy, C_{1-6}alkylthio, C_{1-6}alkylS(=O), C_{1-6}alkyloxy-carbonyl, halo, polyhaloC_{1-6}alkyl, C_{2-6}alkenyloxyamino, R^5-C(=O)-C_{1-6}alkyloxyamino, a radical of formula (c) or (e-1) or (e-2), imidazolyl, triazolyl, tetrazolyl optionally substituted with imino, isoxazolidinyl optionally substituted with hydroxy, isoxazolidinone.

4. A compound as claimed in any one of claims 1 to 3 wherein L is -X-R^3 wherein R^3 is 2,4,6-trisubstituted phenyl.

5. A compound as claimed in any one of claims 1 to 4 wherein the moiety in the 2 position of the pyrimidine ring is a 4-cyano-anilino group, L is -X-R^3 wherein R^3 is a 2,4,6-trisubstituted phenyl, Z is N or C-Y with Y being halo or hydrogen and Q is

hydroxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkyl, halo, polyhaloC_{1-6}alkyl, aminocarbonyl, mono- or di(C_{1-4}alkyl)aminocarbonyl, cyano or Het.

6. A compound as claimed in any one of claims 1 to 5 wherein the compound is
4-[[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-hydroxymethyl]-2-pyrimidinyl]amino]benzonitrile;
4-[[[6-chloro-4-(2,4,6-trimethylphenylamino)]-1,3,5-triazin-2-yl]amino]benzonitrile;
4-[[[6-trifluoromethyl-2-(4-cyanophenylamino)]-4-pyrimidinyl]amino]-3,5-dimethylbenzonitrile;
6-[(4-cyanophenyl)amino]-4-[(2,4,6-trimethylphenyl)amino]-1,3,5-triazine-2-carboxamide;
4-[[[5-bromo-4-(4-cyano-2,6-dimethylphenoxy)-6-methoxymethyl]-2-pyrimidinyl]amino]benzonitrile;
4-[[[5-bromo-4-(4-cyano-2,6-dibromophenoxy)-6-hydroxymethyl]2-pyrimidinyl]amino]benzonitrile;
2-[(4-cyanophenyl)amino]-6-[(2,4,6-trimethylphenyl)amino]-4-pyrimidine carboxamide;
5-bromo-2-[(4-cyanophenyl)amino]-6-[(2,4,6-trimethylphenyl)amino]-4-pyrimidine carboxamide;
a *N*-oxide, a pharmaceutically acceptable addition salt, a quaternary amine and a stereochemically isomeric form thereof.

7. A compound as claimed in any one of claims 1 to 6 for use as a medicine.

8. The use of a compound as claimed in any one of claims 1 to 6 for the manufacture of a medicament for the prevention or the treatment of HIV (Human Immunodeficiency Virus) infection.

9. The use of a compound as claimed in claim 8 for the manufacture of a medicament for the prevention or the treatment of multi drug resistant HIV infection.

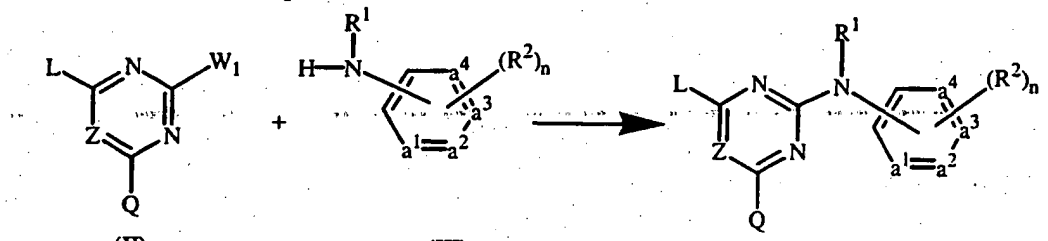
10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 6.

11 A process for preparing a pharmaceutical composition as claimed in claim 10 characterized in that a therapeutically effective amount of a compound as claimed in

any one of claims 1 to 6 is intimately mixed with a pharmaceutically acceptable carrier.

12. A process for preparing a compound as claimed in claim 1, characterized by

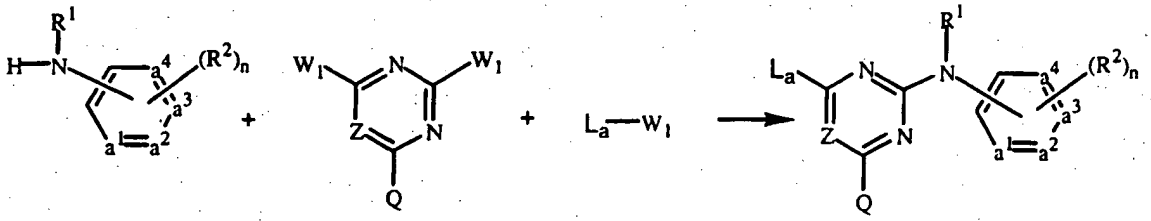
a) reacting an intermediate of formula (II) with an amino derivative of formula (III) optionally under solvent-free conditions or in a reaction-inert solvent under a reaction-inert atmosphere



(II) (III) (I)

with W_1 being a suitable leaving group, and L, Q, Z, R^1, R^2, n and $-a^1=a^2-a^3=a^4-$ as defined in claim 1;

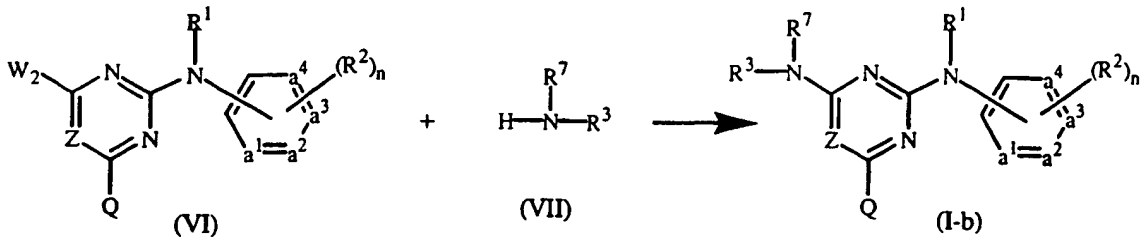
b) by reacting an intermediate of formula (III) with an intermediate of formula (IV) and an intermediate of formula (V) in the presence of a suitable solvent



(III) (IV) (V) (I-a)

with W_1 being a suitable leaving group, Q, Z, R^1, R^2, n and $-a^1=a^2-a^3=a^4-$ as defined in claim 1, and L_a being C_{1-10}alkyl, C_{2-10}alkenyl, C_{2-10}alkynyl, C_{3-7}cycloalkyl, whereby each of said groups may be substituted with one or two substituents independently selected from C_{3-7}cycloalkyl; indolyl or isoindolyl, each optionally substituted with one, two, three or four substituents each independently selected from halo, C_{1-6}alkyl, hydroxy, C_{1-6}alkyloxy, cyano, aminocarbonyl, nitro, amino, polyhalomethyl, polyhalomethyloxy and C_{1-6}alkylcarbonyl; phenyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein each of said aromatic rings may optionally be substituted with one, two, three, four or five substituents each independently selected from the substituents defined in R^2;

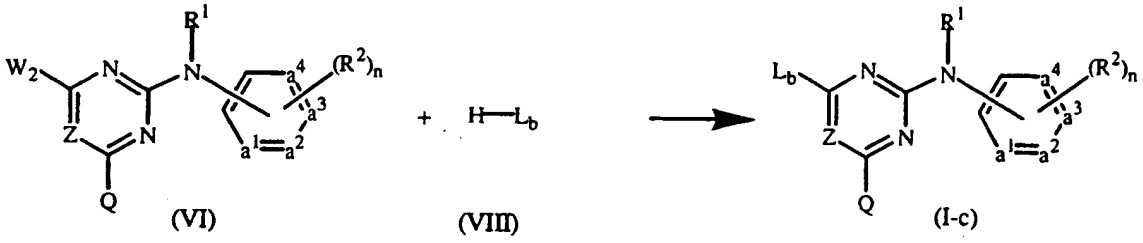
c) reacting an intermediate of formula (VI) with an intermediate of formula (VII) under solvent-free conditions or in an appropriate solvent under a reaction-inert atmosphere



(VI) (VII) (I-b)

with W_2 being a suitable leaving group, and Q, Z, R^1, R^2, R^3, R^7, n and $-a^1=a^2-a^3=a^4-$ as defined in claim 1;

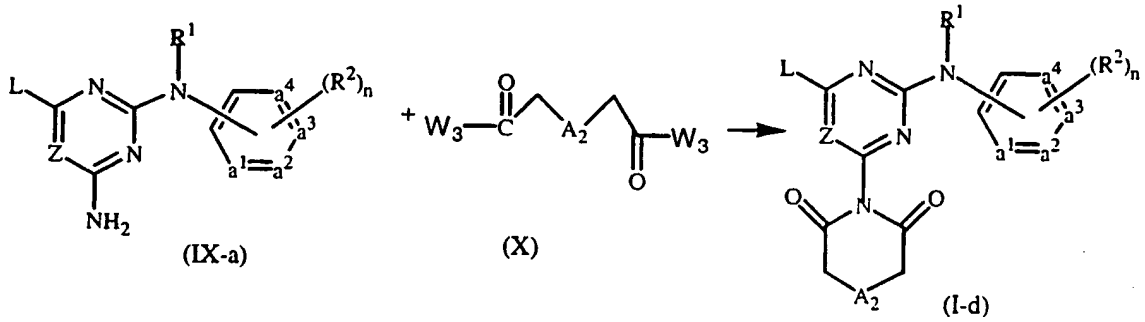
d) reacting an intermediate of formula (VI) with an intermediate of formula (VIII) in an appropriate solvent under a reaction-inert atmosphere in the presence of a suitable base



(VI) (VIII) (I-c)

with W_2 being a suitable leaving group, and Q, Z, R^1, R^2,n and $-a^1=a^2-a^3=a^4-$ as defined in claim 1, and L_b being a radical of formula $-X^1-R^3$ or $-X^2-Alk-R^4$ with X^1, X^2, Alk, R^3 and R^4 as defined in claim 1;

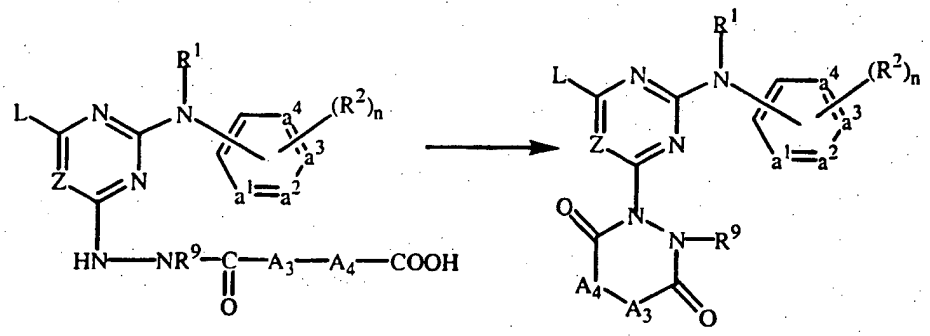
e) reacting an intermediate of formula (IX-a) with an intermediate of formula (X)



(IX-a) (X) (I-d)

with W_3 being a suitable leaving group and L, Z, R^1, R^2, n, A_2 and $-a^1=a^2-a^3=a^4-$ as defined in claim 1;

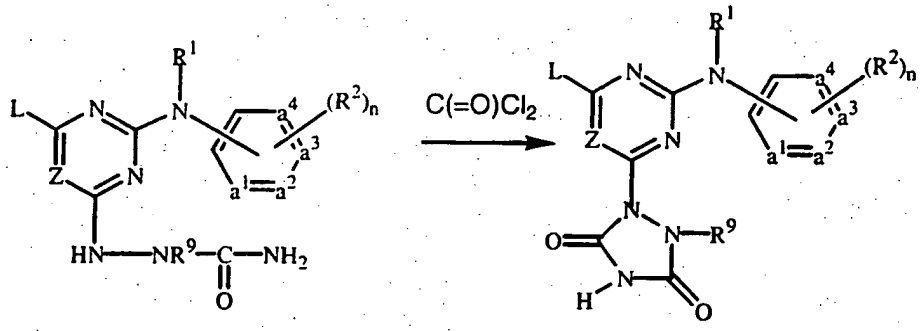
f) cyclizing an intermediate of fomula (IX-b) in the presence of a suitable carbonic derivative and a suitable base



(IX-b) (I-e)

with L, Z, R^1, R^2, R^9, n, A_3, A_4 and $-a^1=a^2-a^3=a^4-$ as defined in claim 1;

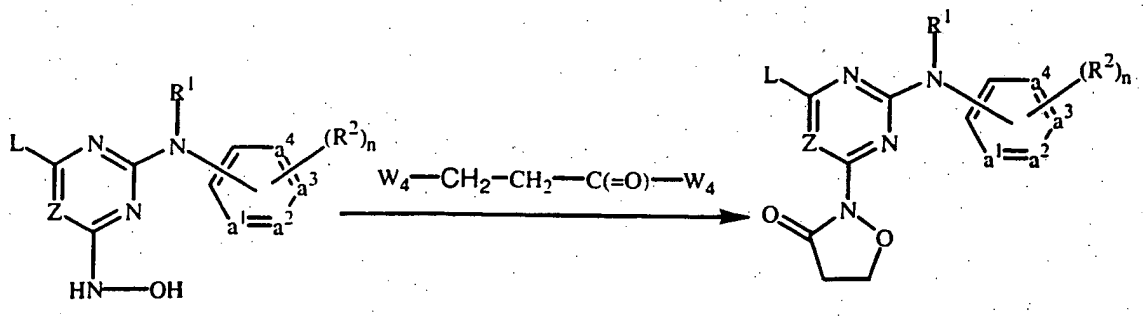
g) reacting an intermediate of formula (IX-c) with a carbonic derivative in the presence of a suitable solvent



(IX-c) (I-e-1)

with L, Z, R^1, R^2, R^9, n, and $-a^1=a^2-a^3=a^4-$ as defined in claim 1;

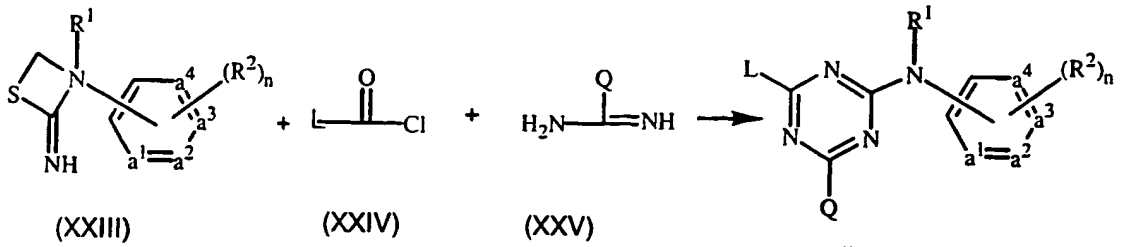
h) reacting an intermediate of formula (IX-d) with W_4-CH_2-CH_2-C(=O)-W_4 in the presence of a suitable base and a suitable solvent



(IX-d) (I-f)

with W_4 being a suitable leaving group and L, Z, R^1, R^2, n, and $-a^1=a^2-a^3=a^4-$ as defined in claim 1;

i) reacting an intermediate of formula (XXIII) with an intermediate of formula (XXIV) and (XXV) in the presence of a suitable base and a suitable solvent



(XXIII) (XXIV) (XXV) (I-g)

with L, Q, R^1, R^2, n, and $-a^1=a^2-a^3=a^4-$ as defined in claim 1;

and, if desired, converting compounds of formula (I) into each other following art-known transformations; and further, if desired, converting the compounds of formula (I), into a therapeutically active non-toxic acid addition salt by treatment with an acid, or conversely, converting the acid addition salt form into the free base by treatment with alkali; and, if desired, preparing stereochemically isomeric forms, *N*-oxide forms or quaternary amines thereof.

13. A product containing (a) a compound as claimed in any one of claims 1 to 6, and (b) another antiretroviral compound, as a combined preparation for simultaneous, separate or sequential use in the treatment of HIV infection.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and as active ingredients (a) a compound as claimed in any one of claims 1 to 6, and (b) another antiretroviral compound.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 November 2001 (15.11.2001)

PCT

(10) International Publication Number
WO 01/85700 A3

(51) International Patent Classification[7]: C07D 239/46, 239/48, 251/50, 251/16, 401/12, A61K 31/505, A61P 31/18

(21) International Application Number: PCT/EP01/04991

(22) International Filing Date: 3 May 2001 (03.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/202,472 8 May 2000 (08.05.2000) US

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
7 February 2002

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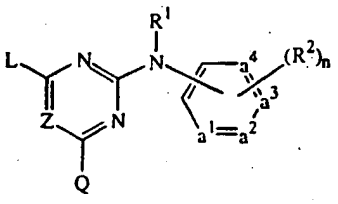
WO 01/85700 A3

(54) Title: HIV REPLICATION INHIBITING PYRIMIDINES AND TRIAZINES



(I)

(57) Abstract: This invention concerns HIV replication inhibitors of formula (I)the N-oxides, the pharmaceutically acceptable addition salts, the quaternary amines and the stereochemically isomeric forms thereof, provided that when Q is halo then Z is N; or when Q is polyhaloC_{1-6}alkyl then Y is hydrogen or C_{1-6}alkyl; their use as a medicine, their processes for preparation and pharmaceutical compositions comprising them.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/04991

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D239/46 C07D239/48 C07D251/50 C07D251/16 C07D401/12
A61K31/505 A61P31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 945 443 A (JANSSEN PHARMACEUTICA) 29 September 1999 (1999-09-29) the whole document ---	1,2,7-13
X	WO 91 18887 A (SMITH-KLINE) 12 December 1991 (1991-12-12) claims; examples 1-38 ---	1,7
X	EP 0 834 507 A (JANSSEN PHARMACEUTICA) 8 April 1998 (1998-04-08) cited in the application the whole document --- -/--	1,2,7-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 November 2001	13/11/2001

Name and mailing address of the ISA	Authorized officer
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